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THYROID NEOPLASMS FOLLOWING IRRADIATION*

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Animal experiments and clinical observations have demonstrated that carcinoma of the thyroid may follow irradiation of the gland. In rats, thyroid carcinomas with metastases have been produced by the administration of ^{131}I (Goldberg and Chaikoff, 1952). If the radioactive iodine or *x*-irradiation is given with a goitrogen, the tumours are more readily produced and a smaller dose of irradiation is effective (Doniach, 1958).

Exposure of the human thyroid gland to ionizing radiation has become increasingly frequent. The isotopes ^{131}I and ^{132}I are widely used in the diagnosis of thyroid disorders, and the former is also employed extensively in the treatment of thyrotoxicosis. In the past, before radioiodine was available, this condition was sometimes treated by *x*-irradiation. Treatment of cutaneous lesions in the neck with radium or *x* rays may lead to some incidental irradiation of the thyroid gland. In some centres it was the practice to irradiate enlarged thymus glands in infancy, and this procedure also inevitably involved the thyroid gland.

There are several reports of carcinoma of the thyroid in man developing after irradiation. It has only rarely been reported after the treatment of thyrotoxicosis by *x*-irradiation (Quimby and Werner, 1949). The findings in children have been of greater significance, and there is now a well-recognized association between irradiation of the cervical and upper thoracic region in infancy and the subsequent appearance of a carcinoma of the thyroid (Duffy and Fitzgerald, 1950; Clark, 1955; Fetterman, 1956; Simpson and Hempelmann, 1957).

In view of the increasing use of radioactive materials, information regarding the development of carcinoma of the thyroid gland following irradiation, either deliberate or accidental, is clearly important. In a previous report three patients who developed carcinomas in these circumstances were briefly described (Kilpatrick, Blomfield, Neal, and Wilson, 1957). Six further patients have now come under observation; in four the diagnosis of carcinoma was clearly established, and in two there was an adenomatous condition of the thyroid presenting some neoplastic features, though a firm diagnosis of carcinoma was not possible. These cases are now reported in detail.

*Based on the opening paper delivered by G. M. W. to the Section of Pathology at the Annual Meeting of the B.M.A., in Birmingham, July, 1958.

Thyroid Carcinomas Following Irradiation

A definite carcinoma of the thyroid has been observed in seven patients following irradiation. Cases 1, 5, and 6 were mentioned briefly in the previous report (Kilpatrick *et al.*, 1957). The doses in these patients have been re-examined. In particular, in Case 5 further information regarding the relative position of the thyroid and radium has resulted in a recalculation which shows a higher dose to the gland than originally reported. The details regarding irradiation dose, latent period, and nature of the neoplasm are summarized in the Table (see next page).

In six patients the irradiation was given in infancy or childhood for the treatment of cutaneous lesions in the neck region, and the details of the original treatment are available. Except in Case 6, the site of irradiation is known from the position of the scar of the original lesion. A calculation of the amount of irradiation received by the thyroid gland has been attempted, and the assumptions on which this has been based are described in the case reports. In three patients (Cases 1, 2, and 6) this did not exceed 300 r.

The interval between the irradiation and the observation of a swelling in the thyroid probably affords the best indication of the latent period, as there was usually a considerable delay before the diagnosis was finally established by surgical exploration and histological examination. In the patients receiving irradiation in the first year of life and subsequently developing a carcinoma the latent period in three (Cases 1, 2, and 4) was under 10 years, but in Case 3 the swelling was apparently not observed until she was 18 years old. In Cases 5 and 6 the irradiation was given in adolescence, and the latent periods were 8 and 17 years. In all these patients irradiated in childhood the carcinoma was predominantly papillary in type, though some follicular arrangement was apparent in Case 4. In four (Cases 1, 2, 4, and 5) the skin lesion was localized on one side of the neck, and in them the thyroid swelling first appeared and the spread of malignant tissue was most extensive in the lobe of the gland immediately adjacent to the irradiated area. In one patient (Case 3) the cutaneous lesion was in the midline and the carcinomatous nodule was situated behind the scar. Case 6 had extensive irradiation of the front of the neck and there was involvement of both sides.

Details of Cases

Case	Sex	Age at Time of Irradiation	Diagnosis and Site of Irradiation	Method of Irradiation	Estimated Maximum Dose to Thyroid	Age at Surgical Biopsy of Thyroid	Interval Between Irradiation and First Sign of Goitre	Type of Neoplasm
1	F	2 months	Naevus on right mandible	Radium	130 r	10 years	9 years	Papillary carcinoma
2	F	3 ,,	Naevus on right side of neck	*X*-ray	100 r	12 ,,	8 ,,	,, ,,
		2 years		,,	160 r			
3	F	5 months	Naevus on front of neck	Radium	2,700 r	19 ,,	18 ,,	,, ,,
4	F	3 ,,	Naevus on left side of neck	,,	1,400 r	22 ,,	?5 ,,	Papillary and follicular carcinoma
		6 ,,		,,	1,300 r			
5	M	12 years	Keloid on right side of neck	,,	1,000 r	25 ,,	8 ,,	Papillary carcinoma
		13 ,,		,,	1,700 r			
6	F	14 ,,	Eczema of neck	*X*-ray	150 r	31 ,,	17 ,,	,, ,,
		16 ,,		,,	150 r			
7	F	26 ,,	Thyrotoxicosis	,,	?>2,000 r	63 ,,	37 ,,	Anaplastic carcinoma
8	F	3 months	Naevus on left side of neck	Radium	?>1,000 r	27 ,,	17 ,,	Papillary adenoma
9	F	21 years	Thyrotoxicosis	*X*-ray	?>2,000 r	43 ,,	22 ,,	Adenoma

The seventh patient with a carcinoma differed greatly from the others. She was irradiated in adult life for the treatment of thyrotoxicosis, and 37 years later developed an anaplastic carcinoma in contrast to the predominantly papillary type seen in the younger patients.

The available details regarding the irradiation of the initial lesion, and the operative findings and histological features leading to the diagnosis of carcinoma, are described in the following case reports. Treatment has been surgical resection whenever possible, followed in some cases by radiotherapy. In some of the younger patients thyroxine has been given post-operatively to act as a pituitary suppressant, as there is evidence that reduction of thyrotrophin may check the growth of some thyroid carcinomas (Crile, 1956; Thomas, 1957).

Case 1

Female born on March 10, 1938. Treatment with radium was given to a capillary naevus overlying the right mandible, beginning on May 4, 1938, and extending over a period of a year. On each of five occasions irradiation was given with five 5-mg. needles; total radium, 25 mg. for 30 minutes. The needles were applied close to the skin, but the size of the treated area is not precisely known. It is assumed that the area was 4 sq. cm. and the distance of the needles from the skin 0.5 cm. It is thought that the nearest part of the thyroid lay between 1.5 cm. and 3 cm. from the treated area. Assuming average size and development during the first year of life, the naevus received approximately 400 r and the thyroid between 50 and 130 r.

Nine years later, in January, 1947, a swelling in the neck was noted by her mother. On August 24, 1948, a surgical exploration was carried out. The left lobe of the thyroid appeared normal. The right lobe was hard and irregular, and contained a fairly well circumscribed nodule about 1 cm. in diameter. There was some enlargement of the cervical lymph nodes on the right side, and several were removed. Histologically there was a papillary carcinoma of the thyroid with metastases in the lymph nodes.

Deep *x*-ray therapy up to 3,100 r was given to the neck between September 13 and October 15. Several enlarged lymph nodes were present after treatment, but they remained constant in size until 1952, when they began to enlarge. Block dissection of the left side of the neck was carried out on April 8, 1953, and of the right side on June 23. Enlarged lymph nodes on both sides contained papillary carcinomatous metastases.

When she was last seen on July 25, 1957, she was well, with no signs of recurrence.

Case 2

Female born on May 29, 1944. A small naevus was present on the lower part of the right side of the neck (Fig. 1), and this was treated on two occasions by *x*-irradiation. On August 22 the naevus was treated with 400 r, 4 cm. focus skin distance, 45 kV, 1 mm. Al filter, 2.5 cm. diameter. Treatment was repeated on August 21, 1946, when the naevus received 400 r, 15 cm. focus skin distance, 100 kV, 1 mm. Al filter, 3 cm. diameter. Assuming that the nearest part of the thyroid was 2 cm. distant from the point of application of the beam, it is possible that a small fraction of the right lobe received a dose of as much as 260 r, made up of 100 r from the first treatment and 160 r from the second. Some of the rest of the thyroid, including the posterior part of the left lobe, may have received a dose of up to 200 r, made up of 80 r from the first treatment and 120 r from the second, but the majority of the gland probably received a dose of less than 100 r.

In 1952 a swelling in the region of the thyroid was noted by her mother, and this slowly increased in size, particularly on the right side. Some tracheal compression was evident on *x*-ray examination. At operation in November, 1956, the sternothyroid was adherent and bound to a nodular fixed thyroid. The nodules were vascular and hard, and spread extensively into the surrounding structures, especially on the right side. Two biopsies of the gland were carried out, but extensive excision was not possible. The microscopical appearance of both nodules was that of a carcinoma, predominantly of papillary type but showing also some more solid areas of compact acini of thyroid epithelium enclosing no colloid. The larger nodule (right lobe) was almost wholly papillary in structure and had very little capsule of fibrous or normal thyroid tissue. The smaller nodule (left lobe) was enclosed by a fibrous capsule, but there was a definite invasion of the capsule by epithelial growth and

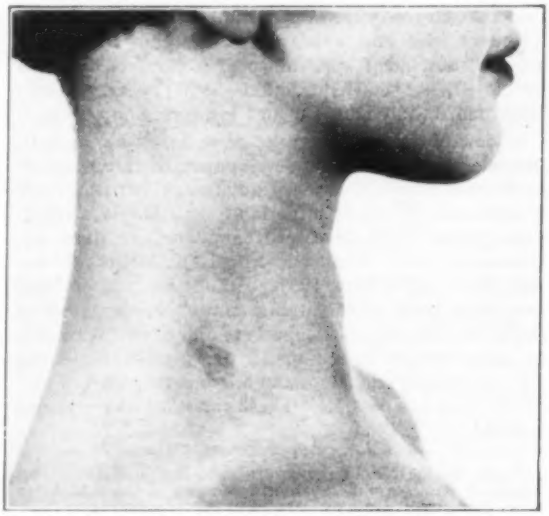

FIG. 1.—Case 2. Showing scar of the small naevus on neck, and the thyroid swelling

possibly invasion of venules. Mitotic figures, though present, were not very frequently seen.

After operation she was given laevothyroxine sodium, 0.1 mg. twice daily, and this was subsequently increased to thrice daily without the development of any signs of hyperthyroidism. The thyroid swelling decreased considerably in size and has become much softer. A repeat *x*-ray examination has shown disappearance of the tracheal narrowing. She was last seen on May 21, 1958, when she was in excellent general health and there was no evidence of any extension of the tumour.

Case 3

Female born on October 20, 1938. A large naevus on the front of the neck, measuring approximately 5.5 cm. in diameter, was treated with radium. On March 18, 1939, 10 1-mg. needles were inserted for 72 hours. The radium plane consisted of an ellipse 5 by 4 cm., seven needles being placed in an outer ring and three in an inner ring. The radium probably covered most of the neck between the jaw and the upper border of the clavicles. Assuming some of the thyroid tissue was in a plane 0.5 cm. below the radium plane and the area was 15 sq. cm., the dose in 72 hours on a basis of 302 mg. hr./1,000 r was approximately 2,300 r. At 1 cm. deep to the radium plane on a basis of 546 mg. hr./1,000 r, the dose was approximately 1,300 r. The irradiation scar in the patient was over and below the thyroid swelling. The dose at the upper limit of the ring of radium needles and 1 cm. deep to the skin may have been 20% greater than quoted above. It may be assumed that the dose on the anterior part of the gland was between 1,300 and 2,700 r.

A swelling was noted in the thyroid in 1956. At operation on May 12, 1957, a round nodular swelling about 3 cm. in diameter was excised from the isthmus and right lobe of the thyroid. Section revealed a pale, fleshy tumour with a few areas of recent haemorrhage. On histological examination there was a fairly well circumscribed papillary adenocarcinoma of the thyroid (Fig. 2). The epithelial cells were mainly cuboidal, but a certain amount of pleomorphism was evident. They formed a single layer around the vesicles and fronds, but in places they were heaped and occasional mitoses were seen. Colloid was restricted to the

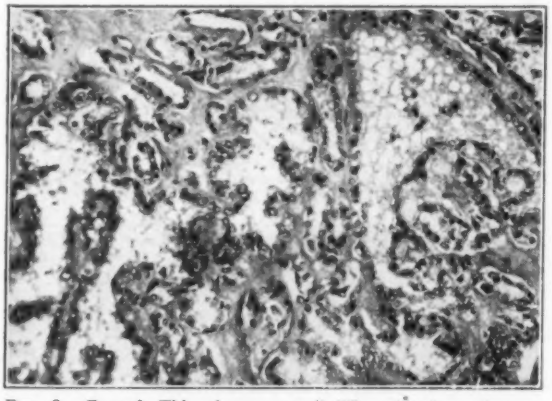

FIG. 2.—Case 3. This shows a well-differentiated carcinoma, mainly of the papillary type. (H. and E. ×116.)

marginal areas of the tumour. There had been some haemorrhage. The capsule consisted of fibrous tissue and compressed normal gland.

Following operation she was treated with laevothyroxine sodium and has remained in excellent health, and when last seen on April 23, 1958, there was no sign of any recurrence.

Case 4

Female born on June 1, 1935. A large naevus was present on the left side of the neck, measuring approximately 7 by 3 cm. (Fig. 3). Two treatments with radium were given.

On August 27, 1935, radium needles were inserted—six 2-mg. and two 1-mg.; total radium, 14 mg. for 36.5 hours. The area of implant was 20 sq. cm. The following estimates and assumptions have been made. (1) The distance from the affected skin to the main mass of the left

FIG. 3.—Case 4. Showing the considerable scarring following irradiation of the naevus and the underlying thyroid enlargement.

lobe of thyroid was 8 mm. and to the extreme edge of the right lobe 22 mm. (2) The needles lay within 5 mm. of the left lobe and were 8 mm. distant from the main mass of the lobe. On this basis the estimated dose to the nearest point of the left thyroid lobe was 1,400 r, to the main mass of the lobe 1,000 r, and to the extreme edge of the gland 400 r.

On December 19, 1936, radium needles were again inserted—eight 2-mg. and three 1-mg.; total radium, 19 mg. for 42.5 hours. The area of implant was 32 sq. cm. It is estimated that on this occasion the nearest part of the left thyroid lobe was 8 mm., the main mass 10 mm., and the extreme edge of the right lobe 40 mm. from the needles. The estimated dose to the nearest point of the left thyroid lobe was 1,300 r, to the mass of the lobe 970 r, and to the extreme edge of the right lobe 230 r.

The total doses from the two exposures to irradiation therefore probably lay in the following range—left lobe 2,000–2,700 r, and right lobe 600–700 r.

A swelling in the left lobe of her thyroid gland was noted in early childhood, probably during the period 1941–3, though no precise date can be given. There was a slow increase in the size of the swelling, particularly during 1957. At operation on September 25, 1957, a hard nodular irregular swelling was present in the left lobe of the thyroid gland and was closely adherent to the strap muscles on the left side of the neck. Metastases were present in the lymph nodes in the left supraclavicular fossa. The tissue was friable and covered with numerous thin-walled vessels. As much as possible was removed, but dissection beneath the strap muscles was extremely difficult, and was abandoned. The right lobe appeared essentially normal.

Histologically there was a mixture of follicular and papillary highly cellular thyroid tissue. A small proportion of the acini contained densely staining colloid, but the cell pattern was highly irregular and many mitotic figures were present. The appearances were those of a fairly well differentiated adenocarcinoma, and the neoplasm merged with a thin peripheral rim of normal thyroid tissue.

Immediately after operation she was given triiodothyronine, 0.02 mg. four times a day, and a week later this was changed to laevothyroxine sodium, 0.1 mg. twice daily and later thrice daily. When last seen, on May 21, 1958, she was in good general health and there was no evidence of further extension of the growth.

Case 5

Male born on June 5, 1923. He was burnt on the right side of the neck when 3 years old and the resultant keloid scar was excised in 1932 and again in 1935. This second excision was followed by radium therapy. Two applications were made externally in sorbo-rubber tubes. On August 1, 1935, 41.5 mg. was applied for 15 hours, and on March 17, 1936, 79 mg. for 13 hours. Assuming the near lobe of the thyroid lay 1 cm. beneath the skin at the point of application of the radium, the right lobe received approximately 1,000 r on the first occasion and 1,700 r on the second. The left lobe received 150 r and 250 r respectively.

A swelling was noted on the right side of the neck in 1944, but this was left undisturbed for four years. On September 21, 1948, a lymph node deep to the right sternomastoid was excised; histology showed a papillary carcinomatous metastasis from the thyroid. On October 6, 1948, a right hemithyroidectomy was carried out together with removal of three more slightly enlarged lymph nodes on the right side of the neck. A nodule about 2 cm. in diameter was embedded in the right lobe of the thyroid gland, and histologically this was a papillary carcinoma. In November, 1948, a course of deep *x*-ray therapy was given to the neck. In 1957 he was well, with no signs of recurrence.

Case 6

Female born on April 26, 1922. On April 8, 1936, she was treated by *x* rays for eczema of the neck, and this was repeated on June 9, 1938. On each occasion the total dose was 300 r by unfiltered *x* rays of 75 kV. It is estimated that the anterior surface of the thyroid received approximately 150 r on each occasion and that the dose to the thyroid tissue 2 cm. from its anterior surface was 60 r.

In 1950 she noticed a swelling in the region of the thyroid gland and was given methylthiouracil for about five months. In November, 1952, this swelling increased in size; she developed some prominence of the eyes and had symptoms suggestive of hyperthyroidism. The swelling on both sides of the neck continued to enlarge. On April 7, 1953, a biopsy of a lymph node from the right side of the neck revealed a papillary carcinoma. At operation on July 1, 1953, the thyroid gland felt extremely hard throughout. The left lobe was removed apart from a thin slice posteriorly. The right lobe was very irregular and was attached to the trachea. The whole right lobe was removed together with a chain of enlarged lymph nodes. Histologically the right lobe contained a papillary carcinoma and the lymph nodes were replaced by this tumour. The left lobe was partially replaced by a papillary carcinoma.

In July, 1954, a swelling of a left supraclavicular gland was discovered, and this continued to enlarge. In November, 1954, 6,000 r was given by cobalt beam to the left supraclavicular region. The gland subsided but later began to enlarge again. On February 18, 1955, several enlarged lymph nodes were excised from the left side of the neck; histologically all contained papillary carcinoma.

When last seen in 1957 she was well, with no signs of any further recurrence.

Case 7

Female born on April 4, 1893. During the period 1918–22 repeated *x*-ray therapy was given to the thyroid for the treatment of thyrotoxicosis. No details of dosage are available, but gross atrophy, scarring, and telangiectasia of skin of neck was produced, particularly over the thyroid isthmus. From what is known of current practice at that time and from the conspicuous cutaneous reaction it is probable that the thyroid gland received more than 2,000 r.

Thereafter she remained well but with some residual enlargement of the gland until 1955, when she noticed an increase in the swelling on the right side. On examination there was a hard nodular enlargement of the isthmus and right lobe. At operation on April 15, 1956, the right lobe of the thyroid was enlarged and adherent to surrounding structures. The left lobe appeared normal. The whole thyroid was removed with the exception of some tissue firmly adherent to the carotid sheath. Histologically there was an undifferentiated anaplastic carcinoma with striking pleomorphism of cells and very numerous mitoses. In May, 1956, there was a recurrence of the swelling on the right side and front of neck, and she was given *x*-ray therapy. She died on November 24, 1956, after continued enlargement of the recurrence in the neck.

Thyroid Adenomas Following Irradiation

In two patients (Cases 8 and 9, in Table I) an adenomatous enlargement of the thyroid was discovered many years after exposure to irradiation. Though an actively hyperplastic condition was present in the glands, there was insufficient evidence to justify a diagnosis of carcinoma. Mitoses were seen in the epithelial cells, but there was no spread outside the capsule of the thyroid or invasion of veins. In Case 8 irradiation of a naevus overlying the left sternomastoid tendon was carried out in early infancy, and subsequently enlargement of the isthmus and right lobe of the thyroid developed. In Case 9 thyrotoxicosis was treated by *x*-irradiation in early adult life and a hard nodular goitre developed 22 years later. The details of these cases are as follows.

Case 8

Female born on August 4, 1930. When aged 3 months she had treatment with radium needles for a naevus overlying the tendinous head of the left sternomastoid muscle. The needles were left in for 36 hours, but other details of the treatment are not available. There is a conspicuous

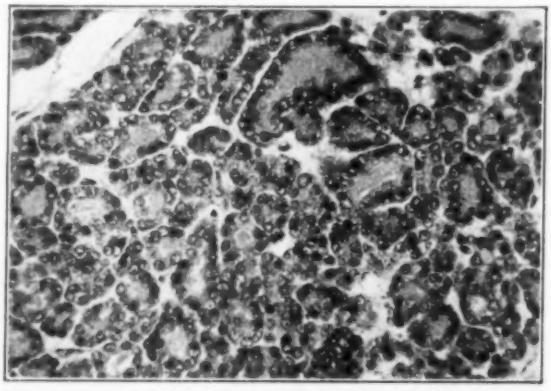

Fig. 4.—Case 8. This part of one adenoma consists of small irregular follicles, lined by cells with large vesicular nuclei and prominent nucleoli. There are occasional mitotic figures. (H. and E. ×200.)

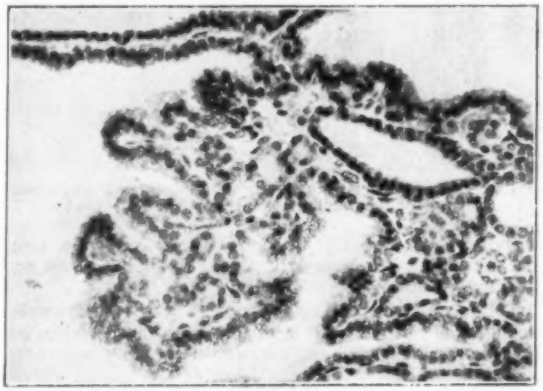

Fig. 5.—Case 8. This is another part of the adenoma seen in Fig. 4. A papillary structure is present. The follicles are distorted and the epithelial cells are moderately pleomorphic. (H. and E. ×185.)

irradiation scar, and comparison with the other similar cases suggests that the thyroid received at least 1,000 r. When aged about 17 years a goitre was noted by her doctor. This slowly increased in size. In December, 1957, a large irregular swelling was present in the isthmus and right lobe of her thyroid gland. At operation on December 19, 1957, the strap muscles and fascia of the neck stripped clearly, revealing the right lobe to be three or four times normal size, soft but not cystic in consistency, and with a normal vascular supply. This enlargement included the isthmus and ended abruptly at the junction with the left lobe. The right lobe and isthmus were excised.

On section of the excised tissue two fleshy nodules were seen, the larger 3 cm. and the smaller 2 cm. in diameter. On histological examination two adenomatous areas were seen compressing the surrounding thyroid tissue and possessing rudimentary and incomplete fibrous capsules. Their structure was that of actively hyperplastic thyroid tissue: the epithelium was cuboidal and surrounded colloid-filled vesicles of the normal range of size. Infolds of epithelium were occasionally seen. A microfollicular structure predominated in parts (Fig. 4). Mitoses in the epithelial cells were fairly frequent. A papillary pattern of growth was seen in some parts of both adenomas (Fig. 5), but the papillary processes usually enclosed colloid vesicles and were invested with a single layer of regular and uniform cells. The thyroid tissue outside the adenomas was more normal, but here, too, mitotic figures were usually frequent in the epithelial cells. A marginal area in one of the sections showed intermingling of thyroid acini, fibrous tissue, and striped muscle, but this probably did not indicate neoplastic invasion. The general features and the absence of anaplasia, vascular invasion, and infiltration of the surrounding tissues preclude a definite histological diagnosis of carcinoma, but the process does seem to be an adenomatous neoplastic condition rather than a simple goitre.

Since operation she has been given laevothyroxine sodium 0.1 mg. thrice daily. When last seen on May 5, 1958, she was well, with no sign of any recurrence of thyroid enlargement.

Case 9

Female born in 1914. She developed a thyroid swelling when she was about 15 years old. When 21 years of age she became unduly nervous, lost weight, and had a rapid pulse rate. A diagnosis of thyrotoxicosis was made, and in 1935 she received about four treatments with *x* rays to the neck. Unfortunately it has not been possible to trace the records of this treatment, and the dose is not known. From what is known of practice at the time it probably exceeded 2,000 r.

In 1955 a lump was noted in the right side of the neck which gradually increased in size. In October, 1957, there was a hard enlargement of the right lobe of the thyroid, narrowing the trachea and displacing it to the left. There was no clinical evidence of hyperthyroidism, and a ^{131}I tracer test showed normal thyroid function.

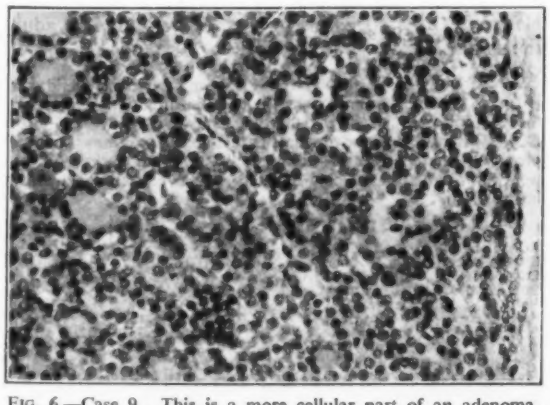

FIG. 6.—Case 9. This is a more cellular part of an adenoma. Only a few small follicles are present. The cells are large and show slight nuclear pleomorphism and sometimes hyperchromatism. Some mitotic figures are evident. (H. and E., ×137.)

At operation on October 23, 1957, the strap muscles and fascial layers stripped easily off the underlying thyroid. The left lobe was approximately of normal size and texture; the right lobe was enlarged four or five times, with a particularly exaggerated upper pole. It was elastic to palpation, with average-sized vessels and without evidence of an extracapsular spread. At its lower pole was a cyst about 1 cm. in diameter. Following ligation of the superior and inferior thyroid arteries a right hemithyroidectomy was performed. The left lobe was left undisturbed. On section the resected portion of the right lobe consisted of several ovoid or spherical masses from 0.5 to 3 cm. in diameter. These were surrounded by a fibrous capsule, sometimes fairly dense; in several parts, however, the capsule consisted only of compressed but otherwise normal-looking thyroid tissue. The structure of the nodules varied greatly, ranging from relatively solid masses of polyhedral cells (Fig. 6) to large colloid-filled follicles lined by cuboidal or slightly flattened epithelial cells. Colloid was relatively scanty in the follicles and in the stroma. The epithelial cells in the nodules had large nuclei, often with prominent nucleoli, and pyknosis was widespread. Mitoses were not infrequent, particularly in the parts where the follicles were small or where the cells formed solid columns. Few intrafollicular projections were present, and scalloping of the colloid was confined to a few follicles. Several large scars and deposits of calcium were present in the stroma.

Though no pathological features were found to suggest that the condition was definitely carcinomatous, the adenomata showed a fairly active hyperplasia. When she was last seen on May 9, 1958, there was no evidence of any local recurrence or metastatic spread.

Discussion

The development of a carcinoma of the thyroid many years after exposure to ionizing radiation constitutes no evidence of a causal relationship; this must be sought on other lines. Most evidence is available with regard to the association between irradiation in childhood and the development of a neoplasm in the thyroid. In reviewing all cases since 1946 of proved carcinoma of the thyroid at the hospitals in Sheffield from which our cases have been drawn, we have found 12 patients developing the condition while under 35 years of age. In six a history of ionizing irradiation of the neck region in childhood was obtained. There is no available information regarding the frequency of exposure of the neck region to irradiation in the general public, but it seems highly improbable that it reaches the level of 50%. In attempting to obtain the past history it is most important that the parents should be interviewed, as the patient may be unaware of previous therapy if it was given in early life for a condition leaving no scar. One patient included in the non-irradiated group developed a thyroid carcinoma when 29 years of age. He gave a history of treatment with "rays" for swollen glands in the neck while in Holland 16 years previously. No details have been traced, but the description of the apparatus given by the parents suggested that the treatment was by ultra-violet rather than *x*-irradiation. A similar high incidence of previous exposure to ionizing radiation among younger patients with thyroid carcinoma has been reported by others (Duffy and Fitzgerald, 1950; Clark, 1955; Fetterman, 1956).

A further indication of a possible association between the irradiation and the development of the carcinoma is that in the five patients with a localized cutaneous lesion the site of the initial and maximal development of the carcinoma was invariably in the underlying part of the thyroid receiving the greatest exposure. In Case 8 the thyroid nodules were situated in the isthmus and right lobe, while the naevus overlay the tendinous head of the left sternomastoid. As,

however, the disposition of the radium needles is not known, no calculation of the exposure of different parts of the thyroid to radiation has been possible in this patient.

More definite evidence has been obtained by following the subsequent medical history of infants subjected to *x*-irradiation of the thymus. Simpson and Hempelmann (1957) found 10 cases of thyroid carcinoma and 7 cases of thyroid adenoma among 1,502 irradiated children, while in 1,933 untreated siblings there was no carcinoma and only one with an adenoma. Their study thus provided strong circumstantial evidence that irradiation in infancy may be an aetiological factor in the pathogenesis of thyroid cancer. Their cases were irradiated for supposed enlargement of the thymus, ours chiefly for skin disorders, particularly naevi. It is, of course, remotely possible, though highly improbable, that the various conditions for which the irradiation was given are all associated directly with an increased liability to develop cancer.

Two further points are noteworthy in our cases of carcinoma following irradiation in childhood. Firstly, the calculated dose to the thyroid gland was low and in three cases did not exceed 300 r. In Case 1 the dose was slightly below the minimum of 180 r reported by Simpson and Hempelmann (1957). Secondly, the latent period in the children is frequently shorter than that seen in carcinoma following irradiation in adult life (Medical Research Council, 1956).

In contrast to the information now available concerning children there is little to suggest that irradiation of the thyroid in adult life may lead to the development of a carcinoma. Indeed, in Case 7 the irradiation for thyrotoxicosis in 1919 and the anaplastic thyroid carcinoma in 1956 might be regarded as fortuitous. Although *x*-irradiation was a recognized method of treating thyrotoxicosis over 40 years ago, reports of cases of thyroid carcinoma following this procedure are remarkably few (Quimby and Werner, 1949). No accurate information is available regarding the frequency of the use of this method of treatment of thyrotoxicosis. In Sheffield it was employed particularly during the years 1931–43, and 99 patients were treated. The latent period for the development of a carcinoma following irradiation in adult life is at least 20 years (Medical Research Council, 1956), and the available evidence in the case of the adult thyroid suggests that it may be much longer. It is thus possible that an association may be noted more often in future years.

The two patients (Cases 8 and 9) presenting nodular adenomas in the thyroid following irradiation are of considerable interest. The histological features suggested considerable cellular hyperplasia : mitosis was frequently seen. However, in the absence of local invasion and metastases the histological appearances alone did not justify a diagnosis of carcinoma. Nevertheless more innocent-looking thyroid adenomas have often been the origin of distant metastases. It is clear from Simpson and Hempelmann's (1957) study that there is an increase in the incidence of thyroid adenomas as well as carcinomas following irradiation. The histology of the two adenomas reported certainly suggests that they should be regarded as premalignant conditions.

It is clearly important to review present practice with regard to exposure of the thyroid to ionizing radiation. It is evident that the increased risk incurred by any individual patient as a result of exposure is very small. It is apparent only when a large survey of irradiated individuals is carried out or when actual cases of carcinoma in younger patients are studied. Doses apparently sufficient to induce neoplastic change are surprisingly small and may be exceeded in certain diagnostic and therapeutic procedures in childhood. On the average, a test dose of ^{131}I resulting in an uptake of 15 microcuries distributed evenly throughout a gland weighing 15 g. or less would deliver a dose to the thyroid of at least 100 r. As, however, the distribution is probably irregular, certain regions would receive a dose considerably in excess of this amount. ^{132}I, with its shorter half-life, delivers a much lower dose. However, the development of satisfactory chemical methods for the measurement of blood iodine (Acland, 1958) should greatly decrease the necessity of using radioactive iodine isotopes. Certainly, in children the use of ^{131}I is only justifiable in exceptional circumstances. Paediatricians, dermatologists, and radiotherapists should appreciate that exposure of the infant thyroid to irradiation may occasionally be followed by the development of a carcinoma. In adults this sequence is apparently less common even though much larger doses are used for therapeutic purposes; but, as the latent period may increase with irradiation in later life, the full effect of increasing use of procedures involving the use of ionizing radiation is not yet apparent. Thyroid carcinoma is a rare condition and accounts for only 0.4% of all deaths from malignant disease (Registrar General's Report, 1954). In cases in later adult life, irradiation is not at present a factor of importance (Kilpatrick *et al.*, 1957). While it is essential to keep the incidence under close observation in order that the precise risks may be more clearly defined, the danger of the use of ^{131}I for the treatment of thyrotoxicosis being followed by a carcinoma of the thyroid appears small and remote.

Summary

Nine cases of thyroid neoplasms are described. In all of them the thyroid gland had been exposed several years previously to ionizing radiation.

In seven patients indisputable histological evidence of carcinoma of the thyroid was present, and in six infiltration outside the gland or metastases had occurred. In six patients the thyroid had been incidentally exposed to irradiation in infancy or childhood during the treatment of cutaneous lesions by radium or *x*-irradiation. In them the dose to the thyroid varied from 130 r to 2,700 r and the latent period from 5 to 18 years. The carcinoma developed in the part of the thyroid exposed to the greatest irradiation. The seventh patient was irradiated for the treatment of thyrotoxicosis when she was 26 years old and had an anaplastic thyroid carcinoma 37 years later.

In two patients a nodular enlargement of the thyroid developed after irradiation. Histologically, hyperplastic adenomatous areas and mitotic figures were seen, but in the absence of local invasion and metastases the histological features alone did not justify a diagnosis of carcinoma. They were regarded as premalignant conditions.

The evidence regarding an association between exposure to ionizing radiation and the subsequent development of a carcinoma is reviewed. Exposure in childhood predisposes to the appearance of thyroid neoplasms. The association following irradiation in adult life is less certain.

We should like to thank Dr. J. L. Emery, of the Children's Hospital, Sheffield, for much valuable information concerning the position and size of the thyroid gland in infancy; Professor D. H. Collins for his advice on the histological sections; and the physicians, surgeons, and radiotherapists who, at various stages, were responsible for the care of these patients and kindly supplied information.

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SURGICAL COLLAPSE DURING AND AFTER CORTICOSTEROID THERAPY*

BY

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Six years ago a man of 34 with rheumatoid arthritis, treated for the previous 18 months with cortisone, had a cup arthroplasty performed on his hip. He developed irreversible shock and died.[1] His death was due to adrenocortical failure consequent on adrenal suppression induced by the exogenously administered corticosteroid. Although attention was drawn at this time to the risks incurred whenever surgery is undertaken during the course of cortisone therapy,[2] there have subsequently been other instances of severe shock developing not only in patients having corticosteroid treatment at the time of surgery but also in those who had stopped treatment weeks or months before.[3-12]

As large numbers of patients have been, or are now being, treated with corticosteroids and may in the future require surgery for their original or some intercurrent condition, it is essential that effective measures to prevent collapse from adrenal failure are widely known, and that, should collapse develop, appropriate treatment is immediately available.

Physiological Considerations

Mechanism of Adrenal Suppression

In both animals and man prolonged administration of adrenocortical hormones reduces the weight of the adrenal glands and may cause adrenal atrophy.[4 13 14] The decrease in anatomical mass is accompanied by loss of physiological sensitivity to pituitary corticotrophin (A.C.T.H.), which can be readily shown by a diminished output of adrenocortical hormones, as compared with a normal gland, after a standard stimulating dose of corticotrophin. This adrenal suppression is due to the exogenously administered corticosteroid inhibiting the release of corticotrophin by the hypophysis, and is in keeping with the concept that the circulating blood level of adrenocortical hormones regulates the rate of corticotrophin release from the pituitary.[14 15]

There is also evidence that prolonged administration of corticotrophin may also inhibit the release of corticotrophin by the patient's pituitary and interfere with the normal responsiveness of the pituitary–adrenal system to a variety of stresses, including surgical trauma.[6 9] Thus injections of corticotrophin induce histological changes in the pituitary similar to those found after prolonged administration of corticosteroids,[16] and collapse has occurred during surgery in patients who have had prolonged treatment with corticotrophin.[9]

Steroids Causing Adrenal Suppression

All the synthetic analogues of hydrocortisone currently available cause pituitary inhibition. On a weight-for-weight basis some have a greater inhibitory action than others, but since the more potent ones, such as prednisone and prednisolone, are usually given in a smaller dosage than the less potent cortisone and hydrocortisone, the resultant degree of pituitary suppression is the same.

Extent of Adrenal Suppression

Adrenal weight reduction and histological changes are only a rough guide to the degree of suppression, which can be assessed more accurately by studying the response of the cortex to stimulation with a standard dose of corticotrophin and measuring the output of adrenocortical hormones.[17 18] Investigations by Jailer and his colleagues[19] suggest that the degree of adrenal suppression may be more related to the duration of corticosteroid treatment than to the dosage. Thus in one patient 100 mg. of cortisone daily for a week induced no detectable adrenal suppression, whereas, in another, 25 mg. daily for ten months produced marked unresponsiveness to corticotrophin stimulation. There are, however, wide individual variations, and, although the cause for this is unknown, it explains why some patients previously treated with steroids react badly to surgery while others do not.

Duration of Adrenal Suppression after Steroid Therapy

In man there are few data on how long adrenal suppression persists after stopping treatment with corticosteroids, and such as there are indicate wide individual variation. Some patients may respond normally to corticotrophin within four days of stopping treatment, whereas Christy *et al.*[19] found in a child of 11, who had had 75 mg. cortisone daily for a year, that 20 units of corticotrophin gel a day for 20 days failed to restore normal adrenal responsiveness.

Clinical experience also shows that there may be a very long delay before normal responsiveness returns. Patients who have stopped steroid treatment for as long as 4½ to 24 months may develop irreversible shock after even minor surgical procedures,[3 4 9] and this led the Mayo Clinic group to advocate special pre-operative preparation for any patient who had had steroid treatment.[4]

Prevention of Adrenal Suppression

Attempts have been made to prevent adrenal suppression during corticosteroid treatment by giving concurrent injections of corticotrophin, but 100 units of high-potency, long-acting corticotrophin gel weekly failed to maintain normal adrenal responsiveness, and 200-300 units weekly were not always effective.[20] Other workers have attempted to restore adrenal activity by giving corticotrophin pre-operatively. This too has not proved a reliable preventive of surgical collapse even when there has been apparent adrenal reactivation as judged by a normal fall in eosinophils.[9] As mentioned above, exogenous corticotrophin may interfere with the pituitary–adrenal response to stress, and adrenocortical failure has been reported following withdrawal of prolonged corticotrophin therapy.[21]

Clinical Considerations

Increased adrenocortical activity appears to be a normal physiological accompaniment of surgical operations.[22-24] In patients with Addison's disease and in those whose adrenals have been suppressed by corticosteroid treatment, minor trauma may precipitate an acute adrenal crisis despite sufficient adrenocortical function remaining to allow a life virtually free of symptoms under more ordinary circumstances. Hence any patient currently having steroid treatment and any who have had prolonged treatment during the previous 12–18 months run a risk of developing acute adrenal insufficiency during or after a surgical operation. These two types of patients constitute an absolute indication for special pre- and post-operative care. Even patients whose steroid treatment ended more than 12–18 months previously probably face an additional operative risk, but usually special pre-operative preparation is unnecessary, provided appropriate action is taken immediately if collapse occurs.

The more severe the operation the greater is the risk, but minor procedures, such as manipulation of a knee or grafting an anal ulcer, may precipitate adrenal insufficiency,[9 12] and special precautions must be taken no matter how trivial the undertaking. Individual variation in the degree of adrenal suppression following steroid treatment is wide, and because 7 out of 36 operations on such patients were performed uneventfully without special preparation is no reason for relaxing this precaution.[25]

Assessment of Adrenal Responsiveness Pre-operatively

The question arises whether useful practical information can be obtained by assessing pre-operatively adrenal responsiveness in patients who have had corticosteroid treat-

*A lecture given at the Faculty of Anaesthetists, Royal College of Surgeons, on June 14, 1958.

ment in the past. The simplest technique is to study the fall in eosinophils following the injection of corticotrophin. More reliable is the increase in urinary or plasma 17-hydroxycorticosteroids after an infusion of corticotrophin or the injection of corticotrophin gel. Although such observations are of considerable interest, they are time-consuming, and impracticable in the case of an emergency operation. The results may even be misleading. Hayes and Kushlan[8] report a patient who had had cortisone for eight months and was prepared for operation with injections of corticotrophin. Judging by the fall in eosinophils the adrenal glands responded normally to corticotrophin stimulation, yet after being anaesthetized the patient became shocked before the incision was made. It is safer to assume the presence of adrenocortical hypofunction and take preventive measures.

Prevention of Adrenal Insufficiency

The first essential preventive step is to know which patients coming to surgery have had or are having corticosteroid therapy, and in every instance this should be a matter for routine inquiry by the house-surgeon. The second is to dispel the still widespread belief that the administration of corticosteroids significantly impairs wound-healing and seriously lowers resistance to infection. It is this belief which has led to steroid treatment being stopped before operation and to fatal post-operative collapse.[10 13] There is, however, good evidence that in appropriate dosage corticosteroids do not significantly interfere with healing or increase the liability to infection.[23] These largely theoretical disadvantages must be weighed against the dangers of adrenocortical insufficiency, and if a hypoadrenal crisis is to be avoided more and not less corticosteroid must be given.

For patients concurrently receiving steroid treatment and for those who have had treatment during the preceding 12–18 months, the amount of additional steroid required will depend upon the severity of the operation and the degree of adrenal suppression. As both factors are difficult to assess, and too small a dose may lead to disaster, larger rather than lesser amounts should be given.

Twenty-four hours and again four hours pre-operatively the patient is given 100–200 mg. of cortisone acetate intramuscularly; and, if currently taking corticosteroids, the patient continues with his usual dose in addition. At the completion of the operation another 100–150 mg. of cortisone acetate is given intramuscularly. Subsequent treatment will depend upon whether the patient is vomiting or not. If possible 50 mg. of cortisone is given by mouth three or four times on the first post-operative day. The dosage is thereafter gradually reduced stepwise over the next week, and stopped altogether after 10–14 days in those not having current steroid treatment, or reduced to the usual maintenance dose in those who are. If the patient is vomiting, intramuscular cortisone acetate will have to be given—100–150 mg. on the first and second post-operative days and 75–100 mg. on the third. Thereafter it is usually possible to revert to oral administration. Throughout the operative period a careful check must be kept on the pulse rate and blood pressure. The development of hypotension or collapse is an indication for increased steroid treatment (see below), and it should be remembered that pyrexia may be a sign of adrenal insufficiency.

This regimen is based on the evidence that a severe stress causes the adrenal glands to secrete the equivalent of 400 mg. of hydrocortisone daily, and that intramuscular cortisone acetate is slowly absorbed—not producing any detectable increase in the plasma steroid level for 6–10 hours, and providing a depot which lasts for several days.

Treatment of Adrenocortical Collapse

For patients who have stopped steroid treatment more than 12–18 months before, it is usually safe to omit pre-operative cortisone coverage provided the treatment outlined below is immediately available if collapse develops during or after the operation. The same measures should be taken if shock occurs in patients already having additional supportive steroid therapy. Provided hypotension is detected early and action taken at once, the patient will respond promptly.[9 12] Because of its slow rate of absorption, intramuscular cortisone or hydrocortisone has no place in the immediate treatment of collapse, nor, because of the uncertainty of the adrenal response, is corticotrophin of value.

The keystone of treatment is intravenous hydrocortisone given as the water-soluble hemisuccinate, 134 mg. of this salt containing 100 mg. hydrocortisone. Here, too, it is wiser to be over-generous in the amount given. As soon as collapse occurs 100 mg. of hydrocortisone is given over two hours by intravenous drip in 500 ml. of 5% glucose. During the first 24 hours 400 mg. of hydrocortisone may have to be infused in 1–1½ litres of fluid. If the hypotension is not corrected quickly, 2–4 mg. of noradrenaline is added to the infusion bottle.

Summary

Corticosteroid therapy, especially if prolonged, causes adrenal suppression. Surgical procedures increase the need for adrenocortical secretions, and may lead to fatal collapse in patients who are currently receiving steroid therapy or who have had such treatment within the previous two years.

To prevent disasters it is essential to know before operation whether the patient is having or has had steroid therapy. Patients currently having steroid treatment need more, not less, corticosteroid during the operative period. They and those who have had steroid treatment during the previous 18 months should be given 100 to 200 mg. of cortisone acetate intramuscularly 24 hours and again 4 hours pre-operatively. Post-operatively 100 to 200 mg. of cortisone is given daily and gradually reduced over a period of a week—by mouth if the patient is not vomiting, by intramuscular injection if he is.

It is usually safe to omit special pre-operative measures in patients who have stopped steroid therapy more than 18 months previously, provided a careful watch is kept on the pulse and blood pressure and, if collapse occurs, immediate treatment is available with intravenous hydrocortisone hemisuccinate in a dose of 100 to 400 mg. per 24 hours.

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BLOOD GROUPS, HAEMOGLOBINS, AND THALASSAEMIA IN TURKS IN SOUTHERN TURKEY AND ETI-TURKS

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The results of a number of surveys of the ABO blood groups of the Turkish population have been published. We do not, however, know of any observations hitherto published on the other blood-group systems. There have been numerous previous publications on thalassaemia in the Turkish population, but the only published work on haemoglobins (apart from isolated cases of sickling) has been that carried out by two of the present authors and their collaborators.

The present survey arose out of the discovery by one of us (Aksoy, 1955) of a focus of sickling among the Eti-Turks, a small Arabic-speaking population living near Mersin, in southern Turkey. The occurrence of thalassaemia and of sickle-cell thalassaemia (Crowley *et al.*, 1957; Aksoy and Lehmann, 1957a; Aksoy, 1958) has subsequently been described in this population. When further investigations were organized the opportunity was taken of carrying out blood-grouping tests on Eti-Turks and of examining a control sample of Turks from the same region. From the Eti-Turks 138 specimens were obtained, of which 108 were examined for blood groups. The specimens were taken from persons attending a hospital out-patient department, and are known to have included an excessive number suffering from haemoglobinopathies. This is unlikely to have affected the blood-group frequencies appreciably, but the inclusion of a number of relatives of patients may have had some slight effect, by exaggerating the frequencies of those genes that happened to be present in these families. Specimens were obtained also from 240 unselected and unrelated Turks, and 108 of these were examined for blood groups.

Blood Groups

Most or all of the specimens were tested for the antigens A_1, A_2, B, M, N, S, C, C^w, c, D, D^u, E, e, Lu^a, K, and Fy^a. The results of our tests and of gene-frequency calculations are given in Tables I–VIII.

TABLE I.—*The A_1 A_2 B O Blood Groups of the Turks of Mersin*

Blood Group	No. Observed	Frequency Observed	Frequency Expected	No. Expected	Gene Frequencies
O	35	0·3241	0·3189	34·44	p_1 .. (A_1) .. 0·2176
A_1	34	0·3148	0·3227	34·85	p_2 .. (A_2) .. 0·0679
A_2	9	0·0833	0·0813	8·78	q .. (B) .. 0·1497
B	20	0·1852	0·1915	20·69	r .. (O) .. 0·5647
A_1B	8	0·0741	0·0652	7·04	
A_2B	2	0·0185	0·0203	2·20	
Total	108	1·0000	0·9999	108·00	Total .. 0·9999

TABLE II.—*The MNS Blood Groups of the Turks of Mersin*

Phenotype	No. Observed	Frequency Observed	Frequency Expected	No. Expected	Chromosome Frequencies
MMS	18	0·1667	0·1508	16·29	MS .. 0·1907
MsMs	9	0·0833	0·0900	9·72	Ms .. 0·3001
MNS	24	0·2222	0·2478	26·76	NS .. 0·0892
MsNs	28	0·2593	0·2521	27·22	Ns .. 0·4200
NNS	10	0·0926	0·0829	8·96	
NsNs	19	0·1759	0·1764	19·05	
Total	108	1·0000	1·0000	108·00	Total .. 1·0000

TABLE III.—*The Rh Blood Groups of the Turks of Mersin*

Phenotype	No. Observed	Frequency Observed	Frequency Expected	No. Expected	Chromosome Frequencies
CCDee	25	0·2315	0·2452	26·48	CDe .. 0·4809
CcDee	35	0·3241	0·3210	34·67	cDE .. 0·1713
CcDEe	21	0·1944	0·1697	18·33	cDe .. 0·0131
ccDEe	10	0·0926	0·1142	12·33	CDe .. 0·0145
ccDEE	3	0·0278	0·0293	3·17	cde .. 0·3203
ccDee	1	0·0093	0·0085	0·92	
Ccddee	1	0·0093	0·0093	1·00	
CCddee	0	—	0·0002	0·02	
ccddee	12	0·1111	0·1026	11·08	
Total	108	1·0001	1·0000	108·00	Total 1·0001

TABLE IV.—*The Lutheran, Kell, and Duffy Blood Groups of the Turks of Mersin*

Phenotype	No. Observed	Frequency Observed	Gene	Frequency
Lu(a+)	3	0·0278	Lu^a ..	0·0140
Lu(a−)	105	0·9722	Lu^b ..	0·9860
K+	4	0·0374	K ..	0·0189
K−	103	0·9626	k ..	0·9811
Fy(a+)	79	0·7383	Fy^a ..	0·4885
Fy(a−)	28	0·2617	Fy^b ..	0·5115

TABLE V.—*The A_1 A_2 B O Blood Groups of the Eti-Turks*

Blood Group	No. Observed	Frequency Observed	Frequency Expected	No. Expected	Gene Frequencies
O	43	0·3644	0·3670	43·31	p_1 .. (A_1) .. 0·2246
A_1	43	0·3644	0·3589	42·35	p_2 .. (A_2) .. 0·0808
A_2	12	0·1017	0·1044	12·32	q .. (B) .. 0·0888
B	14	0·1186	0·1155	13·63	r .. (O) .. 0·6058
A_1B	4	0·0339	0·0399	4·71	
A_2B	2	0·0169	0·0143	1·69	
Total	118	0·9999	1·0000	118·01	Total .. 1·0000

TABLE VI.—*The MNS Blood Groups of the Eti-Turks*

Phenotype	No. Observed	Frequency Observed	Frequency Expected	No. Expected	Chromosome Frequencies
MMS	36	0·3103	0·2614	30·32	MS .. 0·3139
MsMs	7	0·0603	0·0673	7·81	Ms .. 0·2594
MNS	28	0·2414	0·3117	36·15	NS .. 0·0844
MsNs	19	0·1638	0·1776	20·60	Ns .. 0·3423
NNS	10	0·0862	0·0649	7·53	
NsNs	16	0·1379	0·1172	13·59	
Total	116	0·9999	1·0001	116·00	Total 1·0000

TABLE VII.—*The Rh Blood Groups of the Eti-Turks*

Phenotype	No. Observed	Frequency Observed	Frequency Expected	No. Expected	Chromosome Frequencies
CCDee	33	0·2797	0·2958	34·90	CDe .. 0·4916
CCD^{e}ee	0	—	0·0030	0·36	CD^e .. 0·0550
CcDee	42	0·3559	0·3182	37·54	cDE .. 0·1314
CcD^{e}ee	4	0·0339	0·0339	4·00	cDe .. 0·0137
CcDEe	17	0·1441	0·1436	16·94	cde .. 0·3083
ccDEe	6	0·0508	0·0846	9·98	
ccDEE	4	0·0339	0·0173	2·04	
ccDee	1	0·0085	0·0086	1·02	
ccddee	11	0·0932	0·0951	11·22	
Total	118	1·0000	1·0001	118·00	Total .. 1·0000

TABLE VIII.—*The Lutheran, Kell, and Duffy Blood Groups of the Eti-Turks*

Phenotype	No. Observed	Frequency Observed	Gene	Frequency
Lu(a+)	1	0·0086	Lu^a ..	0·0043
Lu(a−)	115	0·9914	Lu^b ..	0·9957
K+	12	0·1034	K ..	0·0531
K−	104	0·8966	k ..	0·9469
Fy(a+)	78	0·6724	Fy^a ..	0·4276
Fy(a−)	38	0·3276	Fy^b ..	0·5724

Observations on the distribution of the ABO blood groups in Turkey by Aygen (1946), Babacan (1937), Irmak (1938), and Onur (1937, 1957) (brought together and tabulated by Mourant *et al.*, 1958) show that nearly all Turkish populations have A-gene frequencies between 24 and 33%, these being on the whole higher than in Eastern Europe apart from Bulgaria and parts of Rumania and Hungary, but also higher than in most other surrounding areas. B-gene frequencies are mostly between 10 and 15%, as in eastern Europe. In conformity with previous findings in the same area we find the Turks of Mersin to have 28.5% of A genes and the Eti-Turks 30.5%. The Turks of Mersin have a B frequency near the top of the normal Turkish range, while the Eti-Turks lie below it. Neither of these populations shows any influence of the neighbouring Yürük nomads (Irmak, 1938) with their very low A and B frequencies, near to those of the Yemenite Arabs and Jews. The frequencies found for the A_2 gene in both the populations which we have tested are surprisingly high, but there are no previous observations in Turkey for comparison and few, if any, on neighbouring populations.

The MNS chromosome frequencies have a typically European aspect. The total frequency of the M gene in the Turks themselves is in fact rather low even for Europe. As Ikin (1958) has pointed out, the rather higher frequency of M in the Eti-Turks and their high frequency of MS may be related to the high M and MS frequencies found in Arabia.

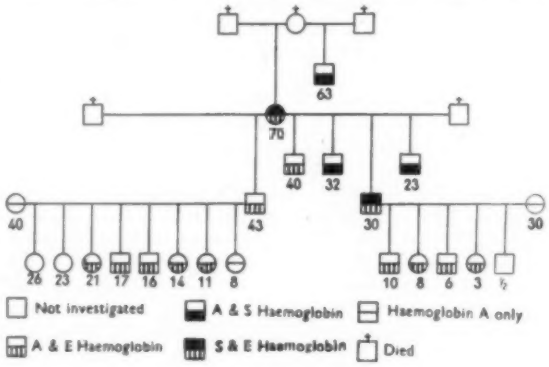
The frequencies of the Rh groups also are essentially European—the rather high frequency of the chromosome CDe and the somewhat low frequency of Rh negatives and of the chromosome cde are typical rather of the Mediterranean area than of northern or central Europe. The relatively high frequency of cDE in both populations, especially the main Turks, seems to be an eastern European characteristic, though found also in Armenians and Iraqi—it is not found in the Mediterranean area as a rule. Perhaps, however, the most important feature of the Rh groups is the very low frequency of the chromosome cDe in both populations, showing a virtual absence of African ancestry, in marked contrast to nearly all other populations so far tested living around or near the eastern Mediterranean. Especially high frequencies have been found in other Moslem populations and attributed to the incorporation in them of negro slaves. The frequencies of the Lutheran (Lu^a), Kell (K), and Duffy (Fy^a) genes are essentially European, but the frequency of Fy^a in the Turks shows a slight tendency towards the high frequencies found everywhere else in Asia.

Abnormalities of Haemoglobin Synthesis

Thalassaemia.—This is well known to occur in Turks (Frank, 1941; Tavat, 1941; Saraçoglu, 1943 (Macedonia); Fakaçelli, 1947; Aksoy, 1950; Aker, 1951; Frank *et al.*, 1951; Römer and Dörken, 1956). Sickle-cell thalassaemia has been reported in Eti-Turks (Aksoy and Lehmann, 1957a; Aksoy, 1958), and some of the subjects in whom the increase of the haemoglobin A_2 fraction associated with thalassaemia has been studied by Crowley *et al.* (1957) were Eti-Turks. Thalassaemia, which is very common in Cypriots generally, has been seen in Turkish-speaking Cypriots (Fawdry, 1944, 1946; Aksoy, 1952), and recently in four Turkish Cypriot families in London (Lehmann, unpublished observations). In 60 haemoglobin samples from Eti-Turks which on electrophoresis showed haemoglobin A as the only adult haemoglobin type, the alkali-resistant fraction was measured by the method of Singer, Chernoff, and Singer (1951); four showed a percentage above 2. It is likely that these blood specimens came from carriers of the thalassaemia gene. As the specimens came from out-patients, who may have included a higher proportion of persons with thalassaemia minor than a true random sample of Eti-Turks, it is likely that the incidence of thalassaemia amongst the Eti-Turks is less than 7%. Of 240 specimens from Turks from the same region only one showed an increase of haemoglobin A_2. However, recently five additional cases of thalassaemia major and several of thalassaemia minor have been observed in this group (Aksoy, 1958).

Sickling.—The first case of sickling in Turkey was reported in a young woman from the island of Marmara (Egeli and Ergun, 1946). The second instance came from Mersin (Küley and Tuna, 1953). Aksoy (1955, 1956) has drawn attention to the high frequency of sickling and of sickle-cell disease in the Eti-Turks living in the southern part of Turkey in and near Mersin, having found the incidence of sickling in 376 hospital out-patients and their healthy relations to be 13.3%. In the present series of 138 Eti-Turks the observed incidence was 46.6%. The specimens were, however, taken from hospital out-patients, many of whom were known to be suffering from sickle-cell disease, and from their relatives. There can therefore, of course, be little doubt that the observed incidence considerably exceeds that which would have been found in a random sample of Eti-Turks. No example of sickle-cell haemoglobin was found among the 240 samples from Turks.

Haemoglobins E and D.—Haemoglobin E was found twice in 138 Eti-Turks. One of them was a haemoglobin E trait carrier (Aksoy *et al.*, 1955), and the other the first instance of sickle-cell haemoglobin E disease (Aksoy and Lehmann, 1957b). After the conclusion of the present survey



The Eti-Turk family with haemoglobins A, S, and E. This pedigree contains some corrections to that previously published in *Nature (Lond.)* (1957). The conclusions then advanced are not affected by these changes.

the family of the woman with sickle-cell haemoglobin E disease was examined and 11 haemoglobin-E trait carriers and one other person with sickle-cell haemoglobin E disease were found (See Fig.). Haemoglobin D was found in one of the 240 Turks tested, and further instances were seen in her family, the members of which are not included in the series of 240 (Aksoy and Lehmann, 1956).

Discussion

Generally speaking, as regards their blood groups, both Turks and Eti-Turks share the characteristics of the peoples of southern and eastern Europe rather than of Asia, and African characteristics are conspicuously absent. The differences between the Turks and Eti-Turks are slight, but, such as they are, they show the Turks, with higher frequencies

of B and Fy^a, to tend perhaps a little more towards Asiatic features than the Eti-Turks, who have, however, the higher frequency of M.

As regards abnormalities of haemoglobin synthesis, we have seen that thalassaemia, as its name implies a Mediterranean character, but not exclusively so, exists in both populations. Sickling, generally regarded as an African character, appears to be extremely rare in Turks and has not been found in the present survey, but is found at a high frequency, almost certainly above 10%, in the Eti-Turks. Haemoglobin E, perhaps derived from south-east Asia, is found sporadically in Eti-Turks, and haemoglobin D has been found in one Turkish family.

The most difficult character to account for is the sickling, in the absence of other African features. The situation in this respect does not appear to differ greatly from that found in the Lake Copais area of Greece (Choremis *et al.*, 1957), and, as in that area, it is possible that a single sickling individual from Africa or elsewhere, or a small number of them, may have introduced the gene for haemoglobin S into a highly malarious area, where the advantage conferred on heterozygotes by this gene in resistance to infection caused carriers of it to multiply selectively.

Summary

The ABO, MNS, Rh, Lutheran, Kell, and Duffy blood-group frequencies of the Turks and Eti-Turks of the Mersin area do not differ greatly from the values commonly found in Europe. Thalassaemia is present in both populations and sickling in the Eti-Turks, in whom its propagation may have been favoured by the prevalence of malaria. Haemoglobin E occurs sporadically amongst the Eti-Turks, and haemoglobin D was found once amongst 240 Turks.

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According to their Annual Report for the year 1957 the British Red Cross Society continued to play a big part in the Hungarian Relief programme during that year. In consultation with the International Committee of the Red Cross, equipment was supplied for two hospitals severely damaged during the rising. In Austria approximately 113,000 refugees were looked after by the Red Cross, the British Red Cross contributing food, clothing, and a certain amount of medical and nursing care in 44 camps.

A BLOOD TRANSFUSION SERVICE IN CYPRUS

WITH NOTES ON THE ABO GROUPS OF CYPRIOTS

BY

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Until 1953 endeavours to establish a blood bank in Cyprus, based on the voluntary system of recruitment of donors, resulted in failure, as volunteers did not come forward in sufficient numbers. The absence of a blood bank was severely felt, since transfusion could be given only when friends and relatives of a patient offered their blood. As no stocks of blood were kept this involved delays in obtaining donors, and grouping, cross-matching, and taking blood immediately before a transfusion could be given, thus causing delays which sometimes resulted in loss of life in an emergency.

In 1953 it was decided to try once again to establish a blood bank. Preliminary attempts to form a panel of donors failed again in spite of all the efforts of the local branch of the Red Cross, so another system of obtaining donors was tried, which proved successful. During almost five years it has functioned through difficult times and many emergencies, and never failed to provide adequate supplies of blood when called upon.

Methods of Founding the Blood Bank

The system employed consisted in laying the onus for providing donors on the medical practitioners who wished to use the services of the bank. Each medical officer in charge of a ward in the hospital was required to open an account by supplying two or more donors, and for each two donors he was credited with one bottle of blood. He was allowed to draw blood from the bank up to the extent of his credit, but overdrafts were permitted at the discretion of the director, or, alternatively, a ward which was overdrawn could borrow from another whose credit was good. In other words, the bank was organized on the same basic principles as an ordinary commercial bank except that interest was not charged on overdrafts.

Donors were drawn from friends and relatives of patients who required a transfusion or who were about to undergo a major operation. Accounts were rendered to each ward every Monday morning.

When the bank was opened there was some reluctance on the part of friends and relations of patients to donate blood. They could not see the necessity for doing so, as there was now a blood bank. Some little trouble had to be taken to impress on them that it was a Cypriot blood bank for Cypriots and that it would have to be supported by Cypriots. (There seemed to be an impression that the European community and young Service men would contribute all the blood necessary.)

Once the initial period of education of the public and the medical profession was over there was no difficulty in obtaining donors and maintaining an adequate stock of blood. Requests then came from private clinics for blood, especially in emergencies, and it was agreed to admit such clinics to participation in all the services of the blood bank on the same terms as the hospital. The service was next extended to the two largest towns, Limassol and Famagusta, and it was hoped to extend it to Paphos eventually. The two other large towns, Kyrenia and Larnaca, dealt direct with Nicosia, and blood was dispatched to them in refrigerated boxes.

All the services of the bank were free, and included provision of blood accompanied by a sterile transfusion set, blood

grouping, typing and cross-matching, Coombs test, and titration for Rh antibodies. The latter two tests had to be relinquished to the clinical laboratory after my departure owing to shortage of staff in the blood bank.

The blood bank is a Government institution, not a public organization, and forms part of the General Hospital, Nicosia, under the administrative direction and control of the medical superintendent, independent of the clinical laboratory and pathologist. I feel that perhaps it is only right to pay a tribute here to the Government of Cyprus for its help and ungrudging financial assistance in developing this institution.

After the blood bank had been in operation a few months it was found that group O donors formed a smaller proportion of the community than had been anticipated (35%), and consequently some care had to be taken to maintain a stock of such blood for emergencies. Nor was this the only unexpected difficulty. Medical practitioners in Cyprus had always maintained that haemolytic disease of the newborn was uncommon in Cyprus, and proof of this was soon obtained in the blood bank, for the number of Rh-negative donors proved to be very low, the lowest in the Mediterranean basin, and it proved almost impossible to maintain a stock of group O Rh-negative blood for emergencies.

From the date of opening the blood bank, very careful records were kept of the name, age, sex, and nationality of each donor, and visits were paid to Paphos, Limassol, and Larnaca to carry out systematic blood grouping until the disturbed state of the island rendered such travelling dangerous. Nevertheless, all races from every part of the island, from mountain villages, the plains, and the sea coast, were tested and recorded so that the figures here presented can be accepted as representative of the Cypriots.

Sera for grouping and typing were obtained by courtesy of Dr. A. E. Mourant from the Blood Group Reference Laboratory in London. The dried serum in glass tubes was forwarded by air freight and kept in a refrigerator until required. Only enough for one or two days was made up at a time. Though A_2 donors were detected, no special record of them was kept, as findings could not be checked by specific sera. All groupings were performed by both direct and indirect methods—namely, donor's cells against known serum and donor's serum against known cells. Cells for reverse grouping were made up every morning: direct grouping was performed by one member of the staff, reverse grouping by another, and the results were compared. Data for Rh frequency were obtained from unselected donors: results of Rh tests for clinical purposes were kept in a separate ledger and not used for statistical purposes. In a series of 2,000 tests the Rh frequency was 2.5% in Greek-speaking Cypriots and 3.2% in Turkish-speaking Cypriots. Thus both communities agree in having the lowest Rh frequency in the Mediterranean basin.

No special study was made of the Rh factor, as only anti-D serum was available.

The ABO Groups of Cypriots

The population of Cyprus and the number of tests performed for statistical purposes are shown in Table I. The number of Armenians, Maronites, and others is too small for statistical investigation and will not be considered further. It was hoped to visit some of the Maronite villages and secure an adequate number for statistical purposes, but unsettled conditions forbade it.

TABLE I.—*Population of Cyprus and Number of Tests Made*

Race	Total No.	No. Tested
Greek-speaking Cypriots	400,000	7,363
Turkish-speaking Cypriots	92,000	2,304
Cypriot Armenians	4,000	57
Maronites	2,000	47
Others	2,000	229
Total	500,000	10,000

The blood groups and gene frequencies of the two main racial stocks in the island are shown in Table II. It will be

TABLE II.—*Blood Groups of Cypriots*

Population	No. Tested	O	A	B	AB	p	q	r
Cypriots, Greek	7,363	35·36	46·36	12·25	6·05	31·1	9·4	59·5
,, Turk	2,304	31·25	46·26	15·66	8·81	31·5	12·0	57·5

observed that both communities show low O frequencies and high A. The p frequency is around 40% and the r 60% or under.

In view of this result the ABO frequencies among the inhabitants of neighbouring countries were examined. These are to be found in a recent publication by Mourant, Kopeć, and Domaniewska-Sobczak (1958), from which the figures in the succeeding tables have been taken unless otherwise stated.

In Anatolia (Table III), 40 miles from Cyprus, blood groups of the inhabitants in 27 different districts have been estimated, but the numbers from each district are usually small; those from European Turkey are larger and more

TABLE III.—*Anatolia*

Author and Date	No. Tested	O	A	B	AB	p	q	r
Onur, 1937	1,152	32·46	40·71	18·58	8·25	28·56	14·46	56·98
,, 1942	815	35·46	43·80	13·99	6·75	29·65	10·96	59·39
,, 1942	1,702	33·43	45·89	12·22	8·46	32·24	10·88	56·88

consistent. The general picture is the same as that in Cyprus—namely, low O, high A, and the gene picture p around 30% and r 60% or under. In the 27 series of observations only three exceptions to this picture are to be found—namely, in Adana and Erzerum districts, where the O frequency is slightly above 40% and the r just above 60%. The Yoruk nomads show quite a different picture, O being over 50% and r 71%. They are probably racially distinct from the other inhabitants.

The figures recorded for Turkey in Europe, including Istanbul, are very similar. Of the four series of figures recorded the highest three are shown in Table IV. No

TABLE IV.—*European Turkey*

Author and Date	No. Tested	O	A	B	AB	p	q	r
Onur, 1942	923	30·66	47·24	13·76	8·34	33·27	11·71	55·02
Babacan, 1937	500	33·80	42·60	14·80	8·80	30·14	12·52	57·33
Aygen, 1946	333	32·73	42·64	17·72	6·91	29·06	13·22	57·72

comment is required other than to say the frequencies present a pattern similar to that seen in Anatolia and Cyprus.

Blood groups of the inhabitants of the mainland to the east of Cyprus may now be considered. Records of 11 investigations into the blood-group frequencies of the Lebanese are recorded, and all, with one exception, show a similar pattern to that in Turkey. The exception is a series of 119 persons in Meshghara in which O was 44.72% and r 77.12%. The largest series of observations, however, is that by Nassif (1953) from the blood bank in the American University Hospital, Beirut. (Not recorded by Mourant.) Nassif says: "The majority of the 5,445 persons whose blood was examined were Lebanese, but samples of Palestinians, Jordanians, and Iraquis were included. Separation into religious groups was not made, although some sects,

TABLE V.—*Lebanon*

Author and Sect	No. Tested	O	A	B	AB	p	q	r
Parr (Assyrian)	161	32·92	41·61	14·91	10·56	30·55	13·54	55·91
,, (Christian)	2,091	37·83	42·37	12·15	7·65	29·12	10·38	60·52
,, (Moslem)	1,777	35·00	36·58	19·13	9·29	26·30	15·31	58·39
Nassif (Mixed)	5,445	36·10	47·25	11·53	5·12	31·00	8·20	60·80

like the Druses, are homogeneous ethnically and deserve separate study. Persons of European, American, and Armenian stock are not included. . . ." Table V shows a pattern similar to the preceding one—that is to say, low O and high A, p about 30%, and r 60% or under.

The inhabitants of the countries in the immediate neighbourhood of Cyprus are undoubtedly Asiatic and predominantly Moslem, though there is a large indigenous Christian Maronite community in Lebanon. In Cyprus the majority of the inhabitants are Christians belonging to the Holy Orthodox Church, commonly referred to as the Greek Church. The language of the church ritual is Greek, as is the language of the Cypriot people who profess Christianity. It would appear, therefore, that the ABO frequencies of the Greeks in Europe would be worthy of study.

A large number of groupings have been performed throughout Greece and the neighbouring islands. Mourant *et al.* list 23 in Greece, 5 in Athens, and 8 in the adjoining islands. Table VI shows the frequencies in three of the largest series from the Greek mainland. The pattern is different from that in the places already considered. The frequencies of O and A are reversed, p is below 26% and r is over 60%.

TABLE VI.—*Greece*

Author and Date	No. Tested	O	A	B	AB	p	q	r
Papamarkou, 1939	10,000	40·63	39·60	15·20	4·55	25·34	10·45	64·21
Constantoulis, 1957	6,378	44·39	37·93	12·93	4·75	24·27	9·26	66·47
Markianos, 1957	6,327	45·03	38·56	11·82	4·58	24·57	8·56	66·87

The three series tabulated are the three highest listed by Mourant *et al.*, but among the others are some curious exceptions to the general pattern. For example, the O frequencies are given as 14 and 15% in two, and some others give the frequency as 35 to 37%. The numbers examined, however, are small and statistically unreliable. The figures from Athens, on the other hand, are large and statistically reliable; moreover, the results are remarkably constant—so much so that it is unnecessary to tabulate them. Of 42,000 persons tested in Athens 42 to 44% belonged to group O; 38 to 39% to group A; 24 to 25% to p, and 65 to 67% to r.

The general picture which emerges from these figures is best expressed in Table VII. The difference between the mainland Greeks and the people of the Middle East comprising Anatolia, Lebanon, and Cyprus is clearly demonstrated.

TABLE VII.—*Comparison of Blood Group Frequencies*

Country	O	A	p	r
Cyprus	31–35	46	31	55–59
Anatolia	32–35	40–45	28–32	56–59
European Turkey	30–33	42–47	29–33	55–57
Lebanon	32–37	36–47	26–31	55–60
Greece	40–45	37–39	24–25	64–66
Athens	42–44	38–39	24–25	65–67

Discussion

Since the first world war it has become increasingly recognized that the ABO blood-group frequencies of a population are of considerable value for determining genetic relationships. The pioneer investigations of Hirszfeld and Hirszfeld during and after the war showed that the group frequencies varied widely between one population and another, and their observations have been confirmed by many studies made since then. For example, Mourant (1954) showed that the Basque population in Spain differ from their neighbours not only in language but also in their blood-group frequencies. The blood-group frequencies in Iceland resemble those of Scotland, Ireland, and North Wales, and are quite different from those of the Norwegians, though the Icelandic people are supposed to be descended from them. Icelandic people have told me they are not descended from the Vikings, who died out, but from the numerous Celtic people whom they brought to Iceland as slaves after their raids and who eventually outlived and outnumbered their masters. It is unnecessary to quote further examples. They are numerous, and would form in themselves a subject for a thesis.

The small island of Cyprus has been the prey of conquerors since before recorded history. The language of the majority of the inhabitants is Greek, but, as Mourant (1954) says, language is a cultural not a genetic factor. Storrs (1949), with reference to Cyprus, says "a common linguistic origin of several thousand years ago is no more than an academic fact." According to Luke (1957), "the blood of Cyprus's cosmopolitan past was fed, indeed, by many sources, as was his speech a blend of many Greek dialects with other admixtures."

The island was occupied by Phoenicians and by Greek settlers in early historical times. Later it was occupied in turns by Egyptians, Assyrians, and Persians. Eventually it passed under the universal domination of Rome, with Cato and Cicero as its early Roman Governors and Brutus as inspector of finance (Storrs, 1949). But according to Hill (1952), the historian of Cyprus, "at no time has the island of Cyprus been a constituent part of Hellenic Greece." Nevertheless, Luke (1957) says that "by the beginning of our era the cultural and linguistic impress was predominantly Greek," though, he adds, it received something of the culture, arts, and languages of three continents.

The island has been depopulated and recolonized a number of times since the fourth century. When the Roman Empire was divided "it was absorbed along with but not as an integral part of Greece by the Byzantine Empire" (Hill, 1952), and during the fourth century A.D., after depopulation subsequent to drought and famine, St. Helena, mother of the Byzantine Emperor, recolonized it with inhabitants from the neighbouring countries. In A.D. 691 the Emperor carried off all the inhabitants rather than let them fall under Arab rule. The time of their return, or if they returned, is uncertain. In 743 the Caliph carried off many whom he settled in Syria. In all, it suffered from 22 Arab invasions over a period of 200 years. It was occupied by Richard Cœur de Lion during the third crusade, sold by him to the Knights Templar, and then to a French knight who established a dynasty on Western lines which lasted 300 years, after which it was occupied by the Venetians and Genoese. In 1570 it was taken by the Turks, who expelled the "Latins" and restored the Orthodox Church; hence inhabitants who remained Christian entered the Orthodox Church and were considered Greek. In the Ottoman Empire a man was labelled by his religion, so that if he professed the Orthodox faith he was a Greek (Bliss, 1912).

During the Turkish occupation drought and famine caused further depopulation, which, aggravated by emigration to escape taxation, reduced the population to barely 25,000. In 1751 an earthquake, drought, and a plague of locusts caused a famine which drove many of the inhabitants to take refuge on the Asiatic mainland. Again in 1760 plague swept off one-third of the population, which was reduced to 7,000 taxpayers.

As a result of international recognition of Greece in 1832 many Orthodox Cypriots went to Athens to obtain Greek citizenship, which was readily granted, and then returned to Cyprus with the status and privileges of European nationals exempt from Turkish taxes and tribute. This proceeded to such an extent that the island was rapidly becoming a Greek colony when the Turkish Government took steps to stop it. Finally, in 1878 the Turkish Government transferred the island to Great Britain. Under British rule the population has increased from 150,000 to over half a million at the present day.

As this history shows, there was a constant interchange of population between Cyprus and the adjoining Asiatic mainland for more than two thousand years, and it is not surprising, therefore, that the blood groups of Cypriots resemble those of their neighbours on the Asiatic mainland rather than those of Greece.

Summary

The methods adopted to establish a blood bank in Cyprus are described.

The ABO frequencies of the two main racial stocks in Cyprus are so similar as to suggest a common ethnic derivation.

The ABO frequencies in Cyprus resemble those of the inhabitants of the adjacent mainland rather than those in Greece. The resemblance is so close as to suggest that Cypriots are ethnically related to their neighbours on the Asiatic mainland.

I thank Dr. A. E. Mourant for supplies of grouping and typing sera without which this work could not have been carried out. To the staff of the blood bank I am greatly indebted for their unwearying assistance, sometimes under difficult conditions, and in particular to the senior technologist in charge, Miss Melahat Houloussi, more especially for her expert administrative assistance and careful keeping of records.

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THE MECHANISM OF POST-PAROTIDECTOMY GUSTATORY SWEATING (THE AURICULO-TEMPORAL SYNDROME)

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Gustatory sweating—that is, sweating during the eating of food—may occur in the distribution of the auriculo-temporal nerve following parotidectomy, penetrating wounds of the parotid, or suppurative parotitis. It may be associated with flushing of the skin in the same region, though in the cases that we have seen sweating has been the predominant feature and flushing minimal or absent. The syndrome does not develop until some months after the operation or injury, and at times only after some years. Once developed, it appears to persist indefinitely. The degree of sweating varies from a slight dampness to sweating profuse enough to be a minor social embarrassment.

The earliest recorded case is attributed to Duphénix (1757), who is stated to have described the syndrome following drainage of a parotid abscess. Later, Baillarger (1853) recorded a case in which the condition occurred bilaterally after bilateral parotitis, and Weber (1897–8) another following suppurative lymphadenitis in the parotid region. Frey (1923) recorded a case following an infected bullet wound of the parotid, and noted that the sweating corresponded to the cutaneous distribution of the auriculotemporal nerve. The syndrome has since been known as the "auriculotemporal syndrome" or "Frey's syndrome."

The reported frequency of the condition varies, probably depending on the thoroughness with which minor examples are searched for and on the length of follow-up. Freedberg *et al.* in 1948 were able to collect only 35 cases from the literature, but with the increase in parotid surgery in the last decade the condition is now recognized to be common. In a personal series (D.H.P.), 15 out of 42 patients had noted sweating after six months. Moyse (1955) noted its presence in 20 out of 25 patients five years after operation. Laage-Hellman (1957) noted some degree of gustatory sweating or flushing in all but 3 of 123 personal cases.

We have studied 16 selected post-parotidectomy patients, two in detail and 14 in less detail, with the object of eliciting the mechanism and pathways by which gustatory sweating is produced. 10 of the 16 patients showed gustatory sweating. The paper reports the results of our studies. The two cases recorded in detail are:—Case 1: a man of 71 who first noticed profuse gustatory sweating nine months after a left superfacial parotidectomy for adenolymphoma; a minute or so after the taking of food, beads of sweat formed on the left temporal region and ran down towards his neck; there was no flushing. Case 2: a man of 58 who first noticed gustatory sweating six months after a left partial parotidectomy; sweating was less profuse than in Case 1; there was no flushing.

Methods of Investigation

Two standard gustatory stimuli were used, which were found to give repeatable responses: (*a*) chewing moistened cotton-wool; (*b*) sucking an acid drop. The latter was the stronger stimulus. Both methods elicited sweating in positive cases within half a minute, but to obtain the maximum response records were not made until after two minutes.

A permanent record of sweat-gland activity was obtained by the method of Thomson and Sutarman (1953). The area of skin to be studied was cleaned with surgical spirit, and a plastic impression paint containing colloidal graphite was applied evenly with a camel-hair brush. When dry (15–30 seconds) the paint was stripped off with "sellotape" and mounted on a glass microscope slide. Direct photographic enlargements were made from the slides. In these positive prints active sweat glands are shown as black dots, the size and number of the dots being a measure of sweat-gland activity.

Anatomical Considerations (Fig. 1)

The parotid gland is innervated by parasympathetic secretomotor fibres and by vasomotor fibres of the sympathetic nervous system. The nerve supply to the sweat glands of the head and neck is also sympathetic in origin. The parasympathetic nerves to the parotid gland arise in the upper part of the medulla and leave the skull in the glossopharyngeal nerve. They leave this nerve in its tympanic branch which passes back into the cranial cavity to form the lesser superficial petrosal nerve. This nerve passes through the foramen ovale to reach the otic ganglion, where its fibres relay. The post-ganglionic fibres join the auriculo-temporal nerve, and hence pass into the parotid gland.

The sympathetic nerves to the head and neck arise in the upper two thoracic segments and pass up in the cervical chain to relay in the superior cervical ganglion. The post-ganglionic fibres form a plexus around the external carotid artery and its branches, and hence reach the auriculotemporal nerve, from which they are distributed both to the parotid gland and to the sweat glands of the temporal region.

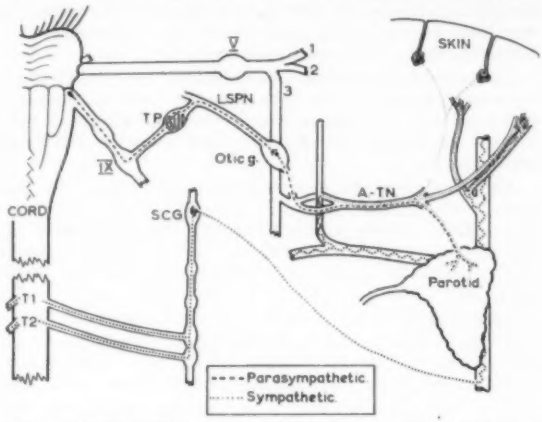

FIG. 1.—Nerve supply to parotid gland and sweat glands. V, trigeminal nerve; IX, glossopharyngeal nerve; T.P., tympanic plexus; S.C.G., superior cervical ganglion; L.S.P.N., lesser superficial petrosal nerve; Otic G., otic ganglion; A.T.N., auriculotemporal nerve.

The auriculotemporal nerve thus contains both sympathetic and parasympathetic fibres which can be differentially blocked by injections of local anaesthetic before they join the nerve. The functions of the two types of fibre can in this way be differentiated.

The Afferent Pathway

Anaesthetization of the mouth with amethocaine reduced but did not abolish gustatory sweating in response to the two standard stimuli. Sweating could be elicited in the absence of jaw or tongue movements by placing in the mouth a wad of cotton-wool soaked in lemon juice. This effect was abolished by previous anaesthetization with amethocaine. It was concluded that the reflex arises in sensory endings both in the mouth and in the muscles of mastication.

Pharmacological Responses of the Involved Sweat Glands

The behaviour of the sweat glands in the affected area was studied following intradermal administration of acetylcholine and atropine. The responses in all cases were compared with those of normal sweat glands in the corresponding region on the other side of the face.

(*a*) *Acetylcholine.*—Acetylcholine was injected intradermally in dilutions varying from 10^{-5} to 10^{-7} (that is, 10 to 0.1 μg./ml.). In Case 1 an injection of 0.05 ml. 10^{-5} acetylcholine (0.5 μg.) produced marked sweating over the injection bleb on the affected side; the same dose on the opposite side evoked no response (Fig. 2). The minimum dose of acetylcholine necessary to produce sweating was determined in all 16 patients studied (see Table). Of the 10 patients with gustatory sweating, 8 showed an increased sensitivity on the affected as compared with the normal side of the order of 10 to 100 times. Of the 6 patients without gustatory sweating, only one showed an increased sensitivity to acetylcholine.

Table Relating Sensitivity of Sweat Glands to Intradermal Injections of Acetylcholine to the Presence of Gustatory Sweating

Case No.	Gustatory Sweating	Concentration of Intradermal Acetylcholine Producing Sweating		Increase in Sensitivity on Side of Opn
		Control Side	Side of Opn	
1	+	10^{-5}	10^{-7}	100 times
2	+	10^{-5}	10^{-6}	10 ,,
3	+	10^{-5}	10^{-7}	100 ,,
4	+	10^{-6}	10^{-7}	10 ,,
5	+	10^{-6}	10^{-7}	10 ,,
6	+	10^{-6}	10^{-7}	10 ,,
7	+	10^{-6}	10^{-7}	10 ,,
8	+	10^{-6}	10^{-7}	10 ,,
9	+	10^{-7}	10^{-7}	1 ,,
10	+	—	10^{-6}	—
11	—	10^{-5}	10^{-6}	10 ,,
12	—	10^{-5}	10^{-6}	1 ,,
13	—	10^{-6}	10^{-6}	1 ,,
14	—	—	10^{-6}	—
15	—	—	10^{-6}	—
16	—	—	10^{-6}	—

(*b*) *Atropine.*—Intradermal injections of 0.2 ml. 10^{-4} atropine (20 μg.) (Cases 1 and 2) abolished gustatory sweating in a localized area around the injection site. An injection of the same bulk of saline had no effect, thus excluding a mechanical explanation.

The Efferent Pathway

The auriculotemporal nerve was blocked in front of the tragus with lignocaine and adrenaline (Case 2). This abolished gustatory sweating. If the nerve fibres mediating gustatory sweating are distributed with sensory fibres in the auriculotemporal nerve, then blocking of this nerve should not only abolish sweating in the temporal region but should also produce skin anaesthesia in the same area. This was found to be the case. These findings were later confirmed by avulsion of the auriculotemporal nerve, which abolished gustatory sweating and left a similar area of anaesthesia. The findings confirm the well-accepted fact that the final path of the efferent arc of the gustatory sweating reflex runs in the auriculotemporal nerve.

The auriculotemporal nerve contains both sympathetic and parasympathetic components. Either component might mediate the gustatory sweating reflex. Further study was made by means of differential nerve blocks.

(*a*) *Sympathetic Block.—Case 2:*—The left cervical sympathetic chain was blocked with 2% lignocaine and adrenaline at the level C 4–5 and at the stellate ganglion. A complete Horner's syndrome was produced, but gustatory sweating was unaffected. *Case 1:*—Simple stellate ganglion block confirmed these findings. From this it was concluded that gustatory sweating was not mediated by the sympathetic pathway responsible for normal thermal sweating. The possible role of the parasympathetic nervous system was therefore investigated.

(*b*) *Parasympathetic Block.*—The otic ganglion lies superficial to the mandibular nerve just below the foramen ovale. At this point it is theoretically possible to block parasympathetic fibres alone (see "Anatomical Considerations" and Fig. 1). *Case 2:*—A needle was introduced above the ramus of the left mandible between the condyle and the coronoid process, and directed medially and upwards until it reached the base of the skull. The patient at this point complained of pain in the jaw, indicating that the needle was in contact with the mandibular nerve. 10 ml. of lignocaine with adrenaline was injected. Within a few minutes there was anaesthesia of the skin over the mandible, and some dullness to pin-prick in part of the auriculotemporal distribution. Gustatory sweating was abolished (Fig. 3, a and b). To demonstrate that this was not due to spread of the block, the patient was heated to induce thermal sweating. Sweating thereupon occurred over the whole body, including the gustatory sweating area (Fig. 3, c). Further tests for gustatory sweating showed that the block persisted for several hours.

From this it was concluded that the fibres concerned in the gustatory sweating reflex pass through the otic ganglion, and are thus similar to those mediating normal gustatory salivation—that is, parasympathetic.

Response to Heating

A heat cradle was placed over the patient (Cases 1 and 2) with a blanket over the cradle to prevent heat reaching the face. Within 30–50 minutes the body temperature was

raised by 1.5° F. (0.8° C.), by which time generalized sweating had occurred. Sweating occurred in both temporal regions, but was less on the affected side.

Discussion

Gustatory sweating in the area of distribution of the auriculotemporal nerve following lesions in the region of the parotid gland must be distinguished both from the sweating which may occur around the lips, nose, and on the forehead in some normal people on eating spicy foods; and from the gustatory sweating which occasionally follows sympathectomy (List and Peet, 1938; Haxton, 1948; Herxheimer, 1958). Gustatory sweating analogous to the auriculotemporal syndrome may also occur in the submandibular region following operation on or near the submandibular gland (Uprus *et al.*, 1934; Young, 1956).

Several theories have been proposed to explain the auriculotemporal syndrome, as follows.

Irritation of the Auriculotemporal Nerve.—Frey (1923) and Needles (1936) suggested that sudomotor fibres are irritated, as they pass through scar tissue in the parotid region, by jaw movements or by swelling of the parotid gland.

Diffusion of a Choline-like Substance.—List and Peet (1938) suggested that acetylcholine or some choline-like substance diffuses from the cut surface of the parotid gland and stimulates sweat glands in the overlying skin.

Hypersensitivity.—Freedberg *et al.* (1948) suggested that the phenomenon might represent the response of denervated and thus hypersensitive sweat glands to "previously unapparent cranial sudomotor impulses."

Aberrant Regeneration.—Ford (1933) postulated that, following damage to the auriculotemporal nerve, aberrant regeneration takes place so that parasympathetic fibres previously innervating the parotid gland come to innervate sweat glands.

Transaxonal Excitation.—Chorobski (1951), discussing the comparable phenomenon of "crocodile tears," suggested that both it and the auriculo-temporal syndrome might be due to "cross talk" between parasympathetic and sympathetic nerve fibres whose insulating sheaths had been damaged.

Frey's theory can be excluded, since gustatory sweating can be elicited by a taste stimulus (lemon juice) in the absence of jaw or tongue movements. The theory of a diffusion of a choline-like substance from the parotid gland can also be excluded, since the syndrome may occur after total parotidectomy.

The theory of hypersensitivity warrants more detailed consideration. That there is an increased sensitivity to acetylcholine of the sweat glands concerned in the auriculo-temporal syndrome has been demonstrated by many workers (List and Peet, 1938; Freedberg *et al.*, 1948; Hogeman, 1951), and confirmed in the present study. The hypersensitivity has been assumed to be due to sympathetic denervation, but, since it does not

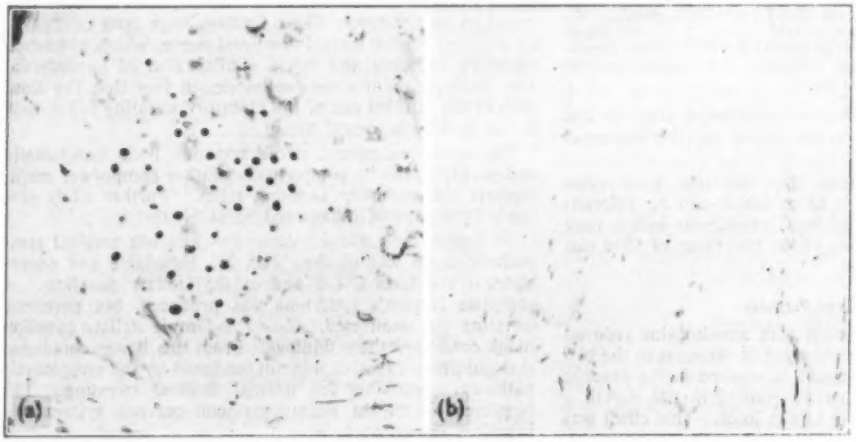

Fig. 2.—Case 1. Sweating evoked (black dots) by local intradermal injection of 0.05 ml. 10^{-3} acetylcholine into (*a*) the auriculotemporal area on the side of the operation, and (*b*) an equivalent area on the normal side.

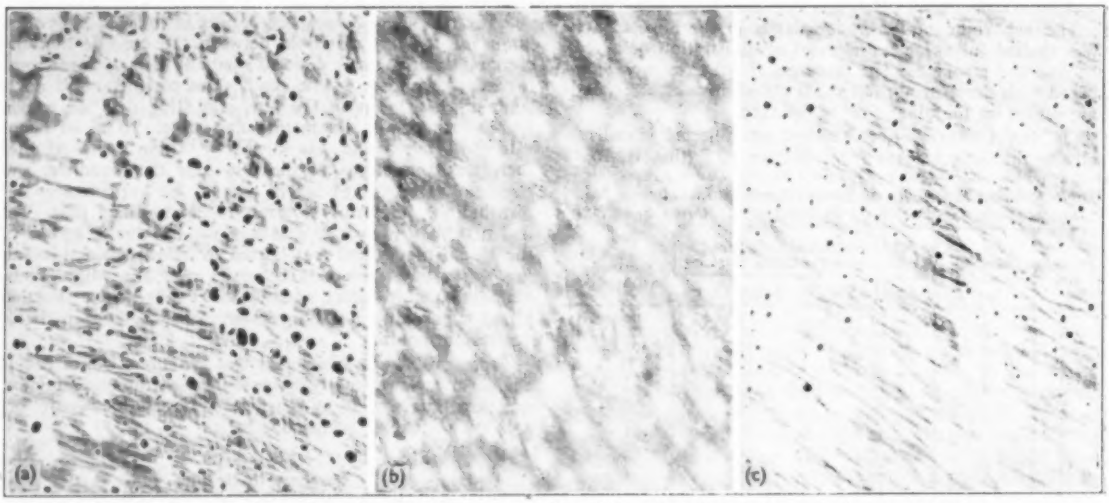

Fig. 3.—Case 2. Records of sweating taken from the same region of the affected auriculotemporal area. (*a*) Gustatory sweating; (*b*) absence of gustatory sweating in same area following otic ganglion block; and (*c*) thermal sweating in same area during otic ganglion block.

occur after formal sympathectomy, either pre- or post-ganglionic (Gardner and McCubbin, 1956), we think it is perhaps better explained by partial sympathetic denervation, the existence of which is shown in these studies by the diminished response of the sweat glands concerned to thermal stimulation. The theory of hypersensitivity by itself is, however, insufficient as an explanation of gustatory sweating, since it fails to explain the dissociation between the responses of the sweat glands to gustatory and thermal stimuli.

We are thus left with the theories of aberrant regeneration and of transaxonal excitation, which are alike in that both postulate that nerve impulses of parasympathetic origin reach sweat glands (Fig. 4). Both would fit the anatomical

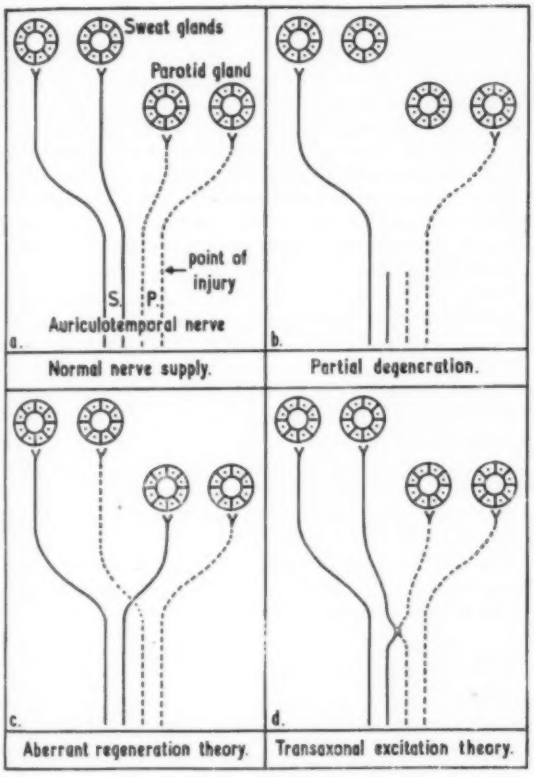

FIG. 4.—Diagram showing theoretical mechanisms of production of gustatory sweating in the auriculotemporal syndrome. Sympathetic fibres (S), continuous line. Parasympathetic fibres (P), broken line.

facts and the experimental observations noted in this study. The auriculotemporal nerve is peculiarly constituted in that, in addition to its sensory fibres, it contains both parasympathetic and sympathetic fibres which leave it to supply adjacent structures. These fibres might be damaged by operation or inflammation in the neighbourhood, and parasympathetic secretomotor fibres at least must be divided when parotid tissue is excised. The rare cases in which gustatory sweating occurs within the area of the great auricular nerve (Hogeman) could be explained by the presence of communicating branches between it and the auriculotemporal nerve. The effects of sympathetic and parasympathetic blocking noted in these studies show that the parasympathetic constitutes the efferent path of the arc, and that parasympathetic fibres must have obtained a functional connexion with sweat glands, which are sympathetic end-organs. This conclusion is confirmed by the observations of Gardner and McCubbin, who cured the auriculotemporal syndrome in two patients by intracranial section of the glossopharyngeal nerve. A functional connexion between parasympathetic nerve fibres and sweat glands is feasible, since post-ganglionic fibres to sweat glands are cholinergic.

If parasympathetic fibres can activate sympathetic structures, then theoretically the converse might occur—that is, sympathetic fibres might activate parasympathetic structures, and the parotid gland obtain a functional connexion with sympathetic fibres formerly innervating sweat glands. In this case a rise in body temperature should produce "thermal salivation." Case 2, a case of partial parotidectomy in which the parotid duct and approximately half of the parotid gland were still present, was suitable for the investigation of this possibility.

Experiment

Saliva was collected simultaneously from both parotid ducts and the effects of gustatory and thermal stimulation were investigated. The results are shown in Fig. 5. Sucking an acid drop produced a marked flow of saliva, the flow from the left gland being about half that from the right; this was to be expected, since part of the left gland had

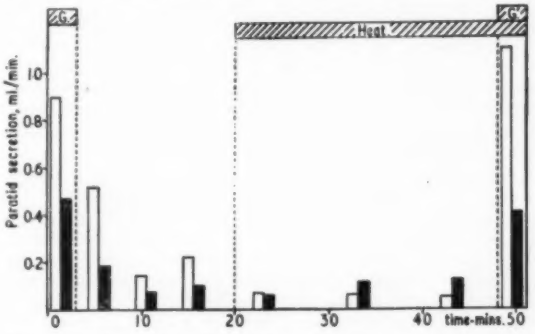

FIG. 5.—Salivary flow from the right normal parotid (white columns) and left operated parotid (black columns) in response to gustatory stimulation (periods G and G') and to a rise in body temperature (period Heat).

been removed. When this response had died away, the patient was heated in a hot-air cradle. The flow of saliva from the normal gland remained at a low level, but that from the operated gland increased until it was twice that from the normal gland. A second gustatory stimulus produced a repetition of the original response despite the continuation of heat stimulation. These results demonstrate "thermal salivation" from the remaining portion of the operated gland and no response to heat from the normal gland, a phenomenon which does not appear to have been previously demonstrated.

The studies on gustatory sweating and the demonstration of thermal salivation prove that some form of cross-connexion between parasympathetic and sympathetic fibres occurs in the auriculotemporal syndrome. On the experimental evidence available up to the present, it is not possible to differentiate with certainty between the "aberrant regeneration" theory and the "transaxonal excitation" theory, both of which could explain the observed phenomena. If the syndrome were found to persist after post-ganglionic cervical sympathectomy and degeneration of the sympathetic fibres, the cross-talk theory would be untenable; but we know of no such case. When, however, the auriculotemporal syndrome is compared with causalgia, which is accepted as due to transaxonal excitation (Granit *et al.*, 1944; Doupe *et al.*, 1944), there are significant differences. Causalgia usually arises early after damage to a nerve and tends towards spontaneous recovery. The auriculotemporal syndrome, on the other hand, does not usually develop for at least some months after the exciting cause, in our cases from three months to three years, but thereafter persists indefinitely. We therefore favour the

aberrant regeneration theory as the explanation of the auriculotemporal syndrome. The degree of hypersensitivity of the sweat glands of the affected areas is probably of importance in determining the severity of the condition once established.

Surgical Considerations

Since the sweating occurs in the distribution of the auriculotemporal nerve, the obvious treatment of this particular variety of gustatory sweating is avulsion of the auriculotemporal nerve. Unfortunately this procedure tends to be followed within a few months by recurrence of the syndrome, presumably from regeneration of nerve fibres. We have recently been trying the effect of prophylactic avulsion at the time of parotidectomy, but, though we are not yet in a position to give full results, one case of gustatory sweating has already occurred. The question arises of why auriculotemporal avulsion is so often only temporarily successful. An observation on a recent case of prophylactic avulsion may provide the answer. A total conservative parotidectomy was being performed, and after completion of the superfacial phase the auriculotemporal nerve was identified and avulsed. As is our practice, the length of the main nerve trunk avulsed was measured and found to be approximately two inches (5 cm.), which was considered to be satisfactory. After the subfacial phase of the parotidectomy had been completed, however, most of the auriculotemporal nerve was found in its normal position in the parotid bed. The apparently satisfactory length of nerve avulsed was an expression of stretching rather than of efficient avulsion.

There are obvious anatomical reasons for the technical inefficiency of auriculotemporal avulsion. The deep surface of the upper pole of the parotid is bound down by dense fibrous adhesions in the region of the temporomandibular joint, and the auriculotemporal nerve runs through these adhesions. Avulsion of the nerve with the parotid or the subfacial parotid *in situ* results in breaking of the nerve at the level of these adhesions. If the procedure is carried out after the whole parotid has been removed, an efficient avulsion back to the otic ganglion should be possible. The demonstration of the technical inefficiency of auriculotemporal avulsion with the parotid *in situ* explains also why this procedure has proved unsatisfactory as a means of suppression of parotid secretion.

In view of the difficulty of dealing with gustatory sweating at the level of the auriculotemporal nerve, the question naturally arises of the possibility of an attack at other levels. Intracranial division of the glossopharyngeal nerve interrupts the parasympathetic fibres concerned, and, as already noted, this procedure has been successfully carried out by Gardner and McCubbin. The magnitude of the operative procedure as compared with the minor character of the disability would, however, seem to rule out this approach apart from very exceptional circumstances. Interruption of the parasympathetic fibres concerned would also occur if the glossopharyngeal nerve were interrupted at the base of the skull before the origin of its tympanic branch. A direct approach to the nerve at this level would be difficult, but an avulsion technique might be feasible and be worth trying. The success of the operation would depend on avulsion of the petrous ganglion.

The investigation has shown that sympathetic interruption has no effect on this type of gustatory sweating, and the final possibility is that of action at the level of the skin. *X*-irradiation can abolish sweating. The dosage required is, however, high, and the danger of skin damage would seem to contraindicate this approach for the treatment of sweating alone. If heavy irradiation were given for other reasons, the abolition of sweating might be expected as a subsidiary advantage. Finally, Laage-Hellman (1958) has recently published full reports of an extensive trial of scopolamine in an aqueous cream base applied locally. With 3% scopolamine he was able to control gustatory sweating, but there was a tendency to dryness of the mouth, presumably due to general absorption, and to dilatation of the pupils from accidental contamination of the eyes. We have tried in two cases the local application before a meal of 1% atropine in an aqueous cream base, but this had no effect on the sweating.

While, therefore, the problem of gustatory sweating is theoretically capable of solution at a number of different levels, further work is required to determine the best solution in practice. In the meanwhile it should be emphasized that the complication, though an annoying one, is of minor importance compared with most of the conditions for which parotidectomy is performed.

Summary

Gustatory sweating in the auriculotemporal area is a common sequel of parotid operations.

Detailed studies have been carried out on two patients with the syndrome and in less detail on a further 14 post-parotidectomy patients, eight of whom showed gustatory sweating.

Gustatory sweating was abolished by blocking the otic ganglion, but was unaffected by blocking the cervical sympathetic. From this it was concluded that gustatory sweating was not mediated by the sympathetic pathway responsible for normal thermal sweating, but by the parasympathetic pathway responsible for normal gustatory salivation.

The theory which best explains the observed facts is that of aberrant regenerating parasympathetic fibres reaching sympathetic end-organs (that is, sweat glands).

The demonstration, we believe for the first time, of the converse phenomenon, thermal salivation, provides further evidence in favour of the theory of aberrant regeneration.

Hypersensitivity to acetylcholine of the partially denervated sweat glands of the auriculotemporal region is present, and its degree influences the severity of the syndrome.

The condition theoretically lends itself to treatment in a number of ways, but more work is required to find a satisfactory practical solution.

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CHRONIC SPLENOMEGALY AND ITS RELATION TO HEPATIC PATHOLOGY*

BY

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The interrelationship between hepatic disease and chronic splenomegaly of apparently unknown aetiology has aroused the interest of numerous observers for well over half a century. Banti in 1894 drew attention to the syndrome of chronic splenomegaly initially associated with fever, anaemia, leucopenia, and occasionally with a history of haemorrhages. Subsequently these cases developed cirrhosis of liver and ascites. Banti postulated the idea of an unknown toxin which acted separately on the spleen as well as on the liver. In his account of the histology of the enlarged spleen he referred to fine widespread fibrosis in the pulp and proliferation of the endothelial cells of the sinuses. These changes gave rise later to macroscopic fibroid nodules—what he called "fibroadenae." This syndrome has also been discussed by Osler (1900) and Warthin (1910). The influence of vascular abnormalities in the portal bed in the pathogenesis of chronic splenomegaly was discussed by McNee (1931), Larrabee (1934), Rouselot (1936, 1949), Thompson *et al.* (1937), Ravenna (1940), and Learmonth (1951).

The role of chronic progressive splenomegaly as the responsible agent in inducing and accelerating fibrotic changes in the liver has been described by many observers. McMichael (1934), who has made the most extensive study of the pathology of the liver and spleen in this group of cases, came to the conclusion that there is no decisive proof that the liver is undamaged in any case of "hepato-lienal fibrosis"; that it is at present impossible to exonerate the liver from the initiation of the pathological process, and that the two organs, liver and spleen, probably suffer simultaneously, although in varying degrees.

Tidy (1952) was of the opinion that the hepatic fibrosis, the chronic splenomegaly, and the haematological changes were due to different and distinct aetiological agents, and made the interesting suggestion that abnormalities of the rhesus factor in the blood between the mother and the offspring, and consequent erythroblastosis foetalis of milder degrees, were probably responsible for development of the syndrome. He denied the benefits of splenectomy in the arrest or reversal of the process.

Sherlock (1955) believed that the hepatic changes were not the sequelae of chronic progressive splenomegaly but were from a different cause.

Milnes Walker (1952) described three types of histological changes in the liver—namely, periportal fibrosis alone, periportal fibrosis with diffuse ramifications between liver lobules, and fully developed fibrosis of the type of subacute hepatic necrosis with nodular hyperplasia, and discussed the different types of clinical manifestations which are associated with each of these types of histological changes.

Chronic splenomegaly is a common clinical entity in many parts of India, particularly in Bengal. Apart from known causes such as protozoal infections, there occurs a group of cases whose aetiology and pathogenesis are not clear even on careful investigation. Such cases have consequently been given the non-committal term of "tropical" or "Bengal" splenomegaly. These cases often give a history of previous malarial attacks. Many of them come from endemic malarious areas. Extensive antimalarial measures in recent times have reduced their frequency to some extent. It is therefore reasonable to think that the initial cause of splenomegaly in most of these cases is probably of malarial origin. However, the progressive enlargement of the spleen after the control and subsidence of the malarial infection is of great interest and remains as yet an unsolved problem.

Many of these cases are associated with clinical and haematological evidences of "hypersplenism." Others give a history of repeated haemorrhages. Still others come with ascites and other evidences of liver disorder.

The pathogenesis of this type of splenomegaly, and particularly the interrelationship of the splenomegaly with the pathological changes in the liver, have not yet been made clear. De (1932, 1937), Menon (1934, 1938), Hughes and Shrivastava (1931), Napier (1939), Sen Gupta (1943), and Chaudhuri (1957) have written on this interesting problem, but have not committed themselves entirely on the pathogenesis of the condition. De, however, postulated the question of a specific toxin elaborated by the spleen as being responsible for the hepatic damage.

From a study of this and other available literature a few significant questions arise. (1) What is the type and frequency of hepatic changes in chronic splenomegaly? (2) What role, if any, has splenomegaly in the initiation, persistence, and progressive increase of the hepatic changes? (3) Conversely, has hepatic fibrosis any role in the splenomegaly itself? (4) Is the hepatic damage an arrestable or reversible process, and can it be arrested or reversed by removal of the hypertrophied spleen?

Methods of Study

For several years we have been interested in this problem of chronic splenomegaly and related hepatic conditions, and have studied our cases according to the following schedule: (1) haematological—examination of the peripheral blood and bone-marrow study; (2) biochemical—examination of plasma proteins and liver function tests; (3) radiological—oesophagogram and splenoportal venogram (Basu and Das, 1956).

At the time of operation opportunity was taken to note the macroscopic appearances of the spleen, liver, and portal venous system, including the presence of collateral venous channels; to estimate the portal venous pressure; and to take a specimen of liver for biopsy. A detailed study of the histology of the spleen and the liver was made from the biopsy material.

After appropriate operative procedures these cases were carefully followed up, and the clinical, haematological, and structural and functional states of the liver were checked up at spaced intervals.

Material

Altogether we have dealt with 72 cases of this type, of which 39 have been studied in great detail from the point of view of liver pathology, and these form the basis of the

TABLE I.—*Categories of Cases*

1. Chronic splenomegaly without evidence of cirrhosis of liver or portal hypertension	1 case
2. Chronic splenomegaly associated with cirrhosis of liver and portal hypertension	22 cases
3. Chronic splenomegaly associated with extrahepatic obstruction	12 ,,
4. Chronic splenomegaly due to specific diseases (kala-azar, 2; haemolytic anaemia, 2)	4 ,,

*Lecture delivered at the Bristol Royal Infirmary, University of Bristol, on March 24, 1958.

present communication. As the result of the overall study as outlined we were able to divide our 39 cases into four categories (Table I).

The cases in group 2 are of immediate interest for the purpose of this paper. The types of hepatic damage met with in this group of cases are given in Table II.

TABLE II.—*Types of Hepatic Damage in 22 Cases*

1. Post-necrotic cirrhosis with nodular hyperplasia	18 cases
2. Post-necrotic scarring	2 ,,
3. Diffuse hepatic fibrosis	2 ,,

In 12 cases in this group the splenomegaly was due to extrahepatic obstruction of the portal venous system, and these included tumours of the pancreas, pancreatic fibrosis, portal venous thrombosis, and congenital cavernomatous transformation of the portal vein. In these cases the histology of the liver biopsy taken at operation showed either a normal parenchymatous pattern or only reticulo-endothelial hyperplasia. Cases associated with kala-azar or haemolytic anaemias also showed reticulo-endothelial cell hyperplasia. In kala-azar cases L.D. bodies were seen in large numbers.

Discussion

A significant finding was the fact that in all the chronic splenomegaly cases where the histology of the spleen showed evidences of congestive changes—namely, dilatation of sinusoids, recent or old evidences of periarterial haemorrhages, and erythrophagocytosis—the liver parenchyma also revealed greater or lesser degrees of fibrosis. The significance of this association as regards the pathogenesis of the splenomegaly is commented upon below.

There was one exception to the usual type of "tropical" splenomegaly in our series. One case of chronic splenomegaly in the absence of any specific cause showed only reticulo-endothelial cell hyperplasia in the spleen. The portal venous pressure in this case was low. The liver did not reveal any evidence of fibrosis.

In conformity with the above findings were the cases of splenomegaly which were associated with extrahepatic obstruction of the portal venous system and also cases of chronic splenomegaly due to specific causes, such as kala-azar or blood dyscrasias—namely, haemolytic anaemias—where fibrosis was conspicuously absent in the liver. The various liver-function tests in this group also showed more or less normal results.

The large majority of cases of hepatic fibrosis were of the type of post-necrotic cirrhosis with large nodules of various sizes enclosed by fibrous reticula. On macroscopic examination at the time of operation, many of these cases showed large bossy nodules on the surface of the liver which were soft in consistency and congested in appearance. Some others showed diffuse granularity. It was not always possible to correlate the naked-eye appearance of the liver exactly with the histological appearance of the biopsy material, but, in general, the degree of fibrosis could be approximately guessed from the consistency and the irregularity of the surface of the liver. The portal venous pressure in these cases was invariably high, and varied between 230 and 480 mm. saline.

The typical Laennec type of cirrhosis, in which there is diffuse hepatic fibrosis enclosing smaller nodules of approximately uniform sizes, was present in only two of our cases. In another two cases there was only post-necrotic scarring, with fibrous septa sparsely distributed among large areas of healthy liver tissue. As is to be expected, the liver-function studies in the last type of cases gave relatively normal results.

From the study of our cases it appears that chronic splenomegaly *per se* has little effect on the histology of the liver and is certainly not responsible for the initiation of the fibrotic process. This is evidenced from the group of splenomegalies due to specific infections or to those due to blood dyscrasias. In one such case, for example, a woman of 30 had progressively increasing splenomegaly due to chronic drug-resistant kala-azar for over 10 years. Splenectomy ultimately helped cure her kala-azar and greatly improved her general health. The liver in this case did not show any evidence of cirrhosis. We also see in our country numerous cases of malarial splenomegaly, which are adequately treated and leave no residual disease either in the spleen or in the liver. Similarly, cases of infrahepatic obstruction of the portal venous system, although associated with chronic splenomegaly, do not show any evidence of functional or structural damage of the liver.

If the splenomegaly *per se* is not responsible for the initiation of the hepatic damage, where are we to look for the noxious agent? This question is difficult to answer, and is perhaps not entirely relevant for this particular discussion. However, as Dible (1951) has pointed out, in England the incriminating influence of viral hepatitis must be seriously considered. In India, too, the influence of virus infection in the morphogenesis of adult cirrhosis is being increasingly stressed (B. K. Aikat, 1957, personal communication), and it may be that the role of the nutritional factor in the pathogenesis of cirrhosis in the tropics has hitherto been unduly emphasized.

Whether the splenomegaly is in any way responsible for the persistence or increase of the fibrotic process in the liver is a moot question. On the evidence available from our cases as well as from the records of others, we are of the opinion that this hypothesis is probably correct. This belief is based mainly on the results of our follow-up studies after operations.

We have performed splenectomies on a large number of cases of fibrocongestive splenomegaly, and spleno-renal shunt operations with splenectomy in a smaller number of cases, and have followed these up very carefully with periodical haematological, liver-function, and liver biopsy studies. The data obtained have been analysed and compared with the pre-operative status. The results of the operations are shown in Table III.

TABLE III.—*Results of Operations*

	Cases
Death before operation	2
Operative mortality	3
Known deaths after operation	4
Lost in follow-up	9
Overall follow-up for periods varying from 6 months to 6 years	54
Clinical condition:	
Cases doing well	46
Cases with recurrence of haemorrhage	5
Cases developing ascites. (They did not have ascites prior to operation)	3
Repeated haematology study (done in 42 cases):	
Cases improved as compared with pre-operative status	36
Repeated liver-function study (done in 31 cases):	
Cases improved as compared with pre-operative status	26
Repeated liver biopsy study (done in 24 cases):	
Cases improved as compared with pre-operative status	16

Of these 72 cases, 41 belonged to the group of chronic splenomegaly which was associated with already existing cirrhosis of liver and evidences of portal hypertension, either manifest by haemorrhages or as actually measured at operation. Only 3 of the 54 cases followed up are known to have developed ascites after operation, and 5 have had recurrence of haemorrhage. 26 out of 31 repeated post-operative liver-function studies and 16 out of 24 repeated post-operative liver biopsy studies show improvement. We have several instances of a long-term follow-up of cases exceeding six years where patients with early cirrhosis of liver and fibrocongestive type of splenomegaly continue to do well after splenectomy and are free from any symptoms. Also there are records where in a short-term follow-up of six months to one year there have been significant changes in the liver-function studies, including reversal of the altered albumin and globulin ratio and also stunting of the pattern of the globulin peak in serum electrophoresis. The histology of the liver has shown satisfactory changes. All these, taken together, point to the fact that the large hypertrophied spleen, besides being inimical to the formed elements of the blood, does adversely affect hepatic function and structure in the pre-existing damaged liver.

How this is brought about is as yet problematical. The hypothetical toxin of the spleen that Banti postulated, and which was also supported by McNee (1931) and Pemberton and Kiernan (1945), can be discounted.

Hunt (1954) has suggested that the excessive splenic effluent in large splenomegalies may be responsible for "idiopathic" portal hypertension. It may, however, well be that this splenic venous hypervolaemia further injures the liver parenchyma by cutting down on the supply of the more important portal venous blood from the intestinal tract. The mean hepatic blood flow has been found in man to range between 1,300 and 1,800 ml. a minute (Ravdin, 1957). Only 25% of this blood normally comes from the spleen. In our large fibrocongestive splenomegalies the splenic effluent as measured in a few cases exceeded 600 ml. a minute. It is possible that, in cirrhosis of the liver, the hepatic parenchyma, already struggling for survival because of the many vascular abnormalities and shunts within the liver, further suffers because of this progressively increasing splenic effluent hypervolaemia, and the process becomes a vicious circle.

The part played by the cirrhotic liver in the pathogenesis of chronic splenomegaly is more easy to understand. There are at least two factors to be considered here. McMichael (1934) made the interesting suggestion that the spleen behaves as the particular drainage lymph node of the liver, and, like other lymph nodes, undergoes hypertrophy in consequence of the inflammatory and necrotic onslaughts affecting the hepatic parenchyma.

In addition, the part played by portal hypertension and the consequent venous stasis, and the effects of such chronic venous stasis resulting from the fibrotic process in the liver, must be considerable, and certainly accounts for the congestive type of splenomegaly that is a constant feature in these cases. The fibrotic process within the liver enhances the portal venous pressure in various ways.

As the result of distortion and disruption of the parenchymal integrity within the liver, abnormal communications develop between branches of the hepatic artery and the portal vein, producing arteriovenous shunts (Popper *et al.*, 1952; Mann *et al.*, 1953), and the high pressure of the systemic arterial circulation is reflected on the low-pressure portal veins, resulting in back pressure and stasis. On this concept is based the rationale of the hepatic artery ligation operation of Rienhoff (1951) and Berman *et al.* (1951). Secondly, the large nodules seen in the post-necrotic type of cirrhosis in our cases can conceivably be expected to obstruct the hepatic venous outflow mechanically and thus enhance portal venous pressure. Thirdly, the effect of the fibrosis itself may be significant, and is more serious when the outflow tract—that is, the central hepatic veins—are interfered with more than the inflow or the portal tracts. The part played by outflow obstruction in the pathogenesis of ascites in cirrhosis has been emphasized in recent years (Madden *et al.*, 1954). That this form of obstruction is also more important from the point of view of portal hypertension has been pointed out by Popper (1952).

In the post-necrotic type of cirrhosis many of the central veins are interfered with by large masses of fibrous tissue, and therefore portal hypertension is likely to be high.

The evidences of congestion in the splenic bed are quite obvious. Besides the enormous dilatation of the sinusoids, the periarterial haemorrhagic areas, etc., two other findings from our series may be mentioned. In many of our cases of large splenomegalies we could find a distinct thrill over the splenic artery at operation that at once stopped on compression of the artery near the hilum. This was therefore an evidence of turbulent flow through the artery, most probably due to intrasplenic arteriovenous communications brought about as the result of enormous sinus dilatation. This type of splenic artery thrill is uncommon in splenomegalies where pulp hyperplasia alone is the predominant element in the histology.

The other finding is the enormous mass of dense tortuous vascular adhesions which bind the spleen to surrounding structures in the fibrocongestive type of splenomegalies, rendering splenectomy in many cases a hazardous process. In contrast, other types of splenomegaly due to specific causes such as the haemolytic anaemias are usually free from adhesions, and splenectomy in such cases is an easy procedure. Obviously the vascular adhesions in the former type are an attempt of nature to compensate for the portal hypertension by creating new portosystemic anastomoses and bypassing the block, which may be either within or outside the liver.

Whether the cirrhotic process in the liver can be arrested to some extent or be reversed by splenectomy has already been partly answered from the experience gained from our series. It must, however, be emphasized that in late stages of cirrhosis of liver with severe functional damage splenectomy, instead of being beneficial, may in fact accelerate hepatic failure. Of this we have had few experiences. This is also to be expected, for, as Smetana (1956) has emphasized, the hepatic cells existing in a precarious balance due to intrahepatic vascular abnormalities in cirrhosis are unduly susceptible to anoxia, either from spontaneous or from operative haemorrhage.

However, it is our belief that splenectomy, with a shunt procedure where necessary, is an eminently suitable operation where the liver damage is not excessive and where hypersplenic manifestations are predominant. This opinion is in accord with the extensive experience of Learmonth (1951) and others. Judged from the clinical and haematological points of view, and from a study of the state of the liver function and of liver pathology of many of these cases before and after operation, there is no doubt that in the large majority the operation has been well worth while and has conferred estimable benefits on the patients.

Conclusion and Summary

I have attempted to review the interrelationship between chronic splenomegaly and the related hepatic pathology from the study of a group of cases which are common in our country and which in the absence of a specific terminology have been called "tropical" or sometimes "Bengal" splenomegaly. The histology of such splenomegalies shows usual fibrocongestive changes, and the liver histology in most cases reveals appearances of post-necrotic cirrhosis, although in a few cases the cirrhotic pattern is of the nature of diffuse hepatic fibrosis or of post-necrotic scarring. Initially such splenomegalies are likely to be of malarial origin and due either to inadequate treatment or to absence of treatment in the early stages; the splenomegaly persists in the long run, although the specific protozoal infection ceases to be manifest.

From a review of these cases and by comparison with other types of splenomegaly due to specific causes, it seems that enlargement of the spleen *per se* has little effect on the histology of the liver. However, once hepatic damage is established, as very commonly happens, the fibrotic and other consequences of such damage induce a state of portal hypertension, with resulting congestive changes in the splenic parenchyma. Along with further increase in the size of the spleen, the splenic effluent markedly increases and further damages the struggling hepatic cells by shunting off the more important effluent from the intestinal tract. A vicious circle is therefore established.

Our experience is that splenectomy at a stage where the cirrhotic process in the liver is not already irreversible cuts across the vicious circle and improves the clinical state of the patient. There is evidence to show that the functional and the structural state of the liver also improve *pari passu*, and the operation therefore can be confidently recommended in selected cases.

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ADDICTION TO UNRESTRICTED DRUGS

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The Pharmacy and Poisons Act, 1933, provides for the registration of sellers of poisons, places poisons in two lists for purpose of sale, and draws up the Poisons Rules under which various schedules of poisons have been arranged, either further restricting their sale or giving exemptions. The Dangerous Drugs Acts, 1920 to 1932, govern the sale of drugs of the morphine and cocaine series. One function of these Acts is to regulate the consumption of those drugs likely to lead to addiction, placing the onus of prescribing the drugs listed on registered medical and dental practitioners.

In the W.H.O. Technical Report Series No. 21 (1950) drug addiction is defined as a state of periodic or chronic intoxication detrimental to the individual, and to society, produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include : (1) an overpowering desire or need to continue taking the drug and to obtain it by any means ; (2) a tendency to increase the dose ; (3) a psychological and sometimes physical dependence on the effects of the drug.

Differentiation is made between addiction-producing and habit-forming drugs—the latter may be taken repeatedly without the production of all the characteristics outlined.

The sale of most drugs known to lead to addiction is governed by the Acts mentioned, but there are a few drugs, thought by many physicians to be "safe," which are not so included. In some cases this is because the drug is comparatively new, since a certain amount of time must elapse after clinical use of the drug has started, before evidence of its danger in this direction is available. Drugs which have been included in the list of scheduled poisons comparatively recently include those of the stimulant group such as benzedrine, and sedatives, such as methylpentynol, known to the lay public as relaxing drugs to allay apprehension. In other cases drugs which have been in use for many years are yet freely obtainable without prescription because they are thought not to be addiction-producing.

This small series of female patients, who have been under our care during the past two years, is described to draw attention to the possibility of addiction to drugs which can be obtained without prescription. That this possibility is not widely recognized is shown by the fact that in several articles in the *Practitioner* between 1951 and 1957 on sedatives and hypnotics (Ström-Olsen, 1951 ; Morgan, 1953 ; Shorvon, 1955 ; Sears, 1956 ; Dunlop, 1957), while the danger of addiction to barbiturates is mentioned, addiction to non-barbiturate hypnotics is not—and their safety is emphasized. Dunlop does point out that sedatives carry with them the danger of dependence and even addiction, but does not deal with the problem except in relation to barbiturates.

The following are the drugs taken by patients in this series, and may all be obtained from a chemist without prescription.

Carbromal is a white crystalline powder, almost odourless and tasteless. The tablets (*B.P.C.*) contain 5 gr. (0.32 g.). It is also made up in proprietary preparations such as "persomnia," containing carbromal 195 mg., and bromvaletone 65 mg. ; "dormiprin," containing carbromal 120 mg., bromvaletone 40 mg., and alkalized aspirin ; and "somnotil," containing chlorbutol 3 gr. (0.2 g.), carbromal 1 gr. (65 mg.), and bromvaletone 1 gr. (65 mg.). It is a mild hypnotic and sedative.

Chlorodyne (tinctura chloroformi et morphinae, *B.P.C.*) contains about 1/64 gr. (1 mg.) of anhydrous morphine in 10 m., as well as small quantities of chloroform, alcohol, and ether. It is used to control cough, vomiting, and diarrhoea.

"*Preludin*" (phenmetrazine hydrochloride) has been in use in this country only since 1955, when it was introduced from Germany for the treatment of obesity. It is a secondary amine, related pharmacologically to the amphetamine group of compounds.

Case 1

While working as a telephonist during the war this patient, unmarried, aged 44, had diarrhoea. She took chlorodyne in normal dosage for this, and found her fears and apprehenions relieved. She continued to take increasing amounts of chlorodyne during the rest of the war period, reaching 3 to 5 bottles a day. This amount produced intoxication and led to her admission to mental hospitals. At various times she attempted to give up the drug but succeeded for only a few months. She then would develop an overpowering urge to start again. The story continues with a four-year period in hospital from 1951 to 1955 and periods in hospital in 1956 and 1957. Even in hospital she would abscond, to be found in a drunken condition some hours later, having drunk two, three, or four bottles of chlorodyne. Her illness has led to her social downfall, to a situation of loneliness, to work much below her capabilities, and to family quarrels. This situation, together with her basic personality of cyclothymic type with periods of

depression, tends to be self-perpetuating. So far there has been no intellectual or moral deterioration. The depressive episodes are not directly related to the drinking bouts.

Diagnosis: cyclothymic personality; depressive episodes.

Case 2

The patient—married, aged 66—suffers from recurrent depressive episodes ushered in by feelings of abdominal discomfort, for which she has taken chlorodyne. She obtains this by going to various chemists, buying it out of her housekeeping allowance and having three bottles a week: she was taking approximately ¼ gr. (16 mg.) of anhydrous morphine daily. At first the patient felt it was doing her good but latterly harming her: "It made me act quite crazy; I could not do without it afterwards." On admission she was in a state of severe depression, with delusions of guilt. There were visual and auditory hallucinations of depressive type. She responded to E.C.T., but relapsed six months later and again started taking chlorodyne; this time she recovered spontaneously. In between attacks there is no evidence of drug-taking. Her personality is shy and retiring. There are occasional mood swings.

Diagnosis: manic-depressive psychosis.

Case 3

This patient—aged 35, married—had a strict upbringing in an upper middle-class family. At 16 her father felt his responsibilities were at an end and he took no interest in her. She got herself a job as governess, and then during the war became a V.A.D. and after that a laboratory technician. She injured her back in a riding accident and had to have several operations. During the last of these, in 1955, she developed feelings of tension and anxiety, and started taking carbromal on the advice of a friend, at first only at night and then during the day, to try to get some sleep. She gradually increased the dose until she was taking 15–20 tablets a day, and would be found staggering round the house, unable to do anything. She was eventually found semiconscious, and was admitted to hospital. There was a period of severe tension, restlessness, and insomnia on stopping the tablets. Personality: anxiety-prone, shy, a poor mixer. No evidence of psychopathic traits.

Diagnosis: anxiety state in immature personality.

Case 4

An unmarried State-registered nurse aged 27, this patient had been in mental hospitals intermittently since completing her training in 1953. She started taking persomnia when she was involved in a coroner's case, though in no way blamed for the death. She felt tense, panicky, took drugs, and woke up in hospital—she was told she had taken an overdose. Since then, whenever she had a job she started taking one or two tablets of persomnia, and gradually increased the dosage until she was found to be ataxic, confused, or somnolent by another member of the staff. The patient has had several jobs since, but always panics and takes drugs—usually persomnia, glutethimide ("doriden"), or carbromal. While in hospital she took 29 tablets of persomnia in an attempt at suicide.

Diagnosis: inadequate psychopath.

Case 5

This woman aged 30 years, married, has been under treatment for at least five years for anxiety symptoms and taking drugs. She states that she first started taking drugs on her doctor's instructions: methylpentynol was prescribed, but she was able to leave the prescription at the chemist's and buy as much as she wanted. She was admitted to one hospital in coma, and afterwards had an epileptic fit and a period of toxic psychosis.

When first seen in 1957, she had been taking chloral and paraldehyde. After stopping all drugs two epileptic fits and a confusional state occurred. While in hospital she managed to bribe someone to bring her in persomnia tablets. After discharge she continued these—25 lasting her two days.

She puts the onus on the psychiatrists to cure her, and asks how she is expected to get better when she can obtain tablets without prescription. She points out that "pep" tablets are advertised in the press.

Diagnosis: hysterical psychopath.

Case 6

A dentist's receptionist—aged 23 years, single—began to take preludin "to slim." She has not become slimmer, but found that the tablets produced a "pepped up" feeling which was very agreeable. To maintain this feeling she had to increase the dose until she was taking between 30 and 60 tablets a day. She became unable to sleep, and kept awake during the day by using the tablets. To keep up the supply she stole from her employer and a considerable sum of money was involved. As a result she lost her employment, and court action was averted by her parents and the dentist's sympathy.

On admission she said she had stopped taking tablets, but on her first week-end out she bought more. She seemed evasive and untruthful, although previously described as generous, good-natured, and impulsive. It seems that since her discharge she has probably continued to obtain tablets, and has made little attempt to tackle her rather difficult life situation.

Diagnosis: immature psychopathic personality.

Case 7

This patient, aged 27 and married, was born in Australia, was trained as a children's nurse, and came to England after her marriage to an Englishman. Disappointed over housing difficulties, she found she could not manage on her housekeeping allowance. She became bored and depressed at home and started using benzedrine inhalers 2½ years ago, but stopped when these were no longer obtainable. About 18 months ago she heard of preludin tablets and started taking two to three daily, but gradually she increased the dosage to ten tablets a day.

She used housekeeping money to buy tablets, got into debt, then stole money from registered letters given to her by her husband to post—these were hire-purchase payments, so her husband soon discovered the failure of payments. He searched the house and found empty bottles representing over £15 worth of preludin.

On giving up the tablets no withdrawal symptoms occurred apart from an increase in depression and anxiety. Her sister was a drug addict.

Diagnosis: immature personality.

Discussion

In each case there was an overpowering need to continue taking the drug concerned, with stealing and lying to obtain it in five cases at least; a tendency to increase the dose, with indifference in the case of the chlorodyne to the exact quantity drunk out of the bottle; and psychological dependence on the drugs. In at least the three patients taking carbromal, and one taking chlorodyne, there was evidence of physical dependence, with an abstinence syndrome on withdrawal. The other patients had already had their drugs stopped before they were admitted to hospital.

One patient who took chlorodyne did so only in the early phase of a depressive psychosis, and in this respect is similar to the cases described by Osberg and Wilder (1955).

Of the drugs dealt with here, reference to addiction can be found only to preludin. While a report by the Council on Pharmacy and Chemistry (1957) states that as yet no cases of addiction have been recorded, Bethell (1957), Clein (1957), and Glatt (1957) each reported a case of toxic psychosis following heavy self-medication. Bethell and

Clein consider that the drug ought to be included in Schedule 1 of the Poisons Rules. To obtain drugs on Schedule 1 the poisons book must be signed, but a prescription is not necessary.

It is not intended here to discuss the details of personality of the patient except in so far as they throw light on the reason for addiction to this type of drug—that is, one obtainable without prescription. It appears that not only must the drug be readily available—as all these are to the entire population—but the patient must be aware of their existence and also be prepared to take the drugs in an experimental fashion. They will take as much as is required to alleviate the symptoms rather than pay heed to warnings on the box about it being dangerous to exceed the stated dose. It is thus people who have some medical or nursing knowledge, and whose knowledge gives them a feeling of confidence, who are likely to take to these drugs. The patients concerned are usually not now working, since they could then obtain barbiturates, but have been connected with the medical, dental, or nursing professions in the past. The high incidence of drug addiction of all kinds among doctors, dentists, and nurses has long been recognized, and this series of patients must be considered as part of the same problem, which is not made easier to solve when the drugs concerned are so readily procurable.

The W.H.O. Technical Report series No. 57 (1952) divides drugs into three groups: (1) morphine and allied groups, with a pharmacological action producing addiction in any person if more than a certain—often small amount—is taken; (2) a group whose pharmacological action never produces compulsive craving, yet is found desirable by some individuals—producing habituation which can be interrupted without significant disturbances; (3) an intermediate group, in which the psychological make-up of the patient is paramount, but the pharmacological action of the drug does play a significant part. The sedatives mentioned here are usually regarded as belonging to the habit-forming group, whereas they should almost certainly be included in the intermediate group. Even if addiction is produced in only a small number of patients, these become much more difficult to treat if they can get supplies of drugs so easily. Fraser and Grider (1953) point out that drug addiction is a "contagious disease" which may spread from an addict to a hitherto drug-free though possibly predisposed person. At least two of these patients started their addiction this way.

Conclusion

It appears, therefore, that all drugs which have a euphoriant or sedative action are likely to cause addiction in predisposed personalities, and the treatment of such patients is made more difficult when such drugs can be freely obtained without any prescription. It is therefore recommended that all such drugs be included in Schedule 4 of the Poisons Rules—that is, can be obtained only on prescription.

In the case of new drugs which have such an action and therefore in all probability will lead to addiction, these should be included in the Scheduled List of Poisons *ab initio*, instead of being sold across the chemist's counter without hindrance until cases of addiction have been described. Vogel *et al.* (1948) point out that ideally the prevention of drug addiction is brought about by developing a people so emotionally sound and well integrated that they will have no need for chemical aids to adaptive behaviour. The second and more realistic approach in our present society is to keep the addiction-prone and the ex-addict from narcotic drugs.

Summary

Attention is drawn to the possibility of addiction, using the W.H.O. criteria, to drugs which may be obtained without prescription.

Seven cases of addiction to such drugs are described.

It is suggested that all drugs which have euphoriant or sedative action may cause addiction and should be placed on the list of Schedule 4 Poisons. They could then be obtained only on prescription.

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CASE OF INFANTILE ULCERATIVE COLITIS

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We record here a case of ulcerative colitis in an infant who is probably the youngest patient suffering from this disease yet reported. The child was barely 3 weeks old when the symptoms first presented.

Ulcerative colitis in infants runs a similar course to that in adults. The disease may present as an acute fulminating attack, as recurrent subacute attacks, or as an insidious progressive unrelenting disease which keeps the patient a constant invalid. However, in infancy the disease seems to be more severe, has a higher incidence of complications, and is less responsive to treatment—a view which accords with that of Bargen and Kennedy (1955).

The diagnosis of infantile ulcerative colitis may be difficult and should be kept in mind when an infant presents with symptoms of persistent diarrhoea, especially if the motions contain blood and mucus. Proctoscopy, sigmoidoscopy, and barium enema will confirm the diagnosis in nearly every case.

In acute disease extensive *x*-ray changes may be apparent in less than two weeks (Hodgson and Kennedy, 1955). In their review they follow Weber and Bargen's (1940) classification and divide their patients as follows. Type 1:—*X*-ray findings positive, the lesion beginning in the rectum and progressing proximally; proctoscopic changes present. This group was the commonest in their series. Type 2:—Proctoscopic manifestations negative or equivocal; *x*-ray evidence of disease present. Type 3:—Unusual proctoscopical appearance with peculiar mucosal pattern and ulcers in the rectum and sigmoid; radiological examination reveals evidence of disease on the right side.

In nearly 95% of cases the disease involves the rectum and most of the colon. A preliminary bacterial examination of the stool is always carried out to exclude a bacillary dysentery.

As regards the prognosis, the younger the child, the more acute the attack, the worse the outlook. Lyons (1956) maintains that the longer the child is able to survive the ravages of the disease the better are his chances. The highest mortality is in the first year of the disease. Long-standing ulcerative colitis is associated with an increased incidence of malnutrition, retardation in development, and advanced pathological changes in the bowel, such as stricture, polyposis, and neoplasm. Except for frank neoplastic changes, prognosis generally is based more on the child's clinical adjustment to the disease than on the gross and microscopical findings in the bowel.

Treatment

Medical measures, except for the complications, seem to afford some relief. Most patients respond with alleviation of their symptoms, yet they never experience complete remissions, nor do they have a normally formed stool (Meeker and Goff, 1956). This presents rather a problem to the clinician in that the child is not entirely well but never ill enough to require surgical intervention. With the advent of steroid therapy it was at first thought that the disease could be held in check, but, except for the very acute fulminating attack, this treatment has in the main proved disappointing.

Active supportive therapy has been found to give the best results. This includes small frequent blood transfusions and parenteral protein and vitamin therapy, and the maintenance of correct fluid, electrolytic, and nitrogen balance.

It is generally conceded that surgery is mandatory in acute toxic ulcerative colitis not responding to medical therapy, and in threatening sequelae: (*a*) perforation, (*b*) stricture, (*c*) arthritis and dermatitis, (*d*) severe growth failure, (*e*) malignant degeneration. In resorting to surgery, an ileostomy alone should be performed only as a temporary emergency measure.

Total colectomy, with or without resection of the rectum, is the operation of choice. Many surgeons are inclined to the more conservative ileorectal anastomosis in the first place, with observation of the rectum at regular intervals by sigmoidoscopy.

Case Report

A male infant aged 3 months, an only child, was admitted to the children's medical ward on December 7, 1955. He had been breast-fed for the first month and then artificially fed. His weight on admission was 11 lb. 4 oz. (5.1 kg.). At the age of 3 weeks the mother first noticed that there was slight pink staining of the napkin by the motion. She also volunteered the information that the child whimpered at each bowel action. The motions were as frequent as two- to three-hourly and were soft and greenish. The child was admitted to a fever hospital on three occasions for investigation of the diarrhoea, and each time was discharged home without a diagnosis having been made. No pathogenic organisms had been cultured from the stools.

The family history revealed nothing relevant. The mother, father, and infant live in one room in the home of the grandparents.

On examination the pulse was 130 and the temperature 99.4° F. (37.4° C.). The baby appeared pale, but lay quietly on the examination couch. There was loss of elasticity of the skin, and the fontanelles were slightly depressed. The respiratory and cardiovascular systems showed no abnormality. Per abdomen the spleen and liver were not palpable, and rectally the sole abnormality was red blood on the examining finger.

Laboratory investigations: Hb, 86%; serum electrolytes normal; direct film of stools showed no parasites, but pus and red cells were abundant, and on culture no pathogenic organisms were grown. Two further stool examinations gave similar findings.

The child's condition continued to deteriorate, the motions were frequent, watery, and blood-stained, and the temperature remained between 100 and 102° F. (37.8 and 38.9° C.). Supportive therapy included small blood transfusions and half-strength Hartmann's solution subcutaneously. After a week the child's weight had dropped 1½ lb. (680 g.).

Changes in feeds were made, but for the next 14 days the child's condition remained *in statu quo*, except that the diarrhoea was much less. A small transfusion of 150 ml. was given. The patient failed, however, to make progress, motions again becoming frequent and bloody. There was now a marked fall in serum electrolytes, especially of the serum sodium. This was rectified by subcutaneous N/6 saline and Hartmann's solution.

A barium-enema examination showed that the descending and proximal sigmoid colons were extremely irritable, resulting in rapid return of the enema. Filling of the colon was obtained only as far as the hepatic flexure. There was persistent spasm of the wall of the descending colon, and the mucosa of the sigmoid and descending colon appeared thickened.

Sigmoidoscopy under anaesthesia revealed a rectum half filled with blood-stained fluid. The mucosa was inflamed, but no ulcers were seen. As a result of these findings laparotomy was decided upon, and, as the child had been prepared for such a contingency, operation was proceeded with (D. L. S.)

Through a lower left paramedian incision the abdomen was explored. The whole of the sigmoid colon was dilated and thickened, as in inflammatory lesions such as ulcerative colitis. Numerous small glands were present in the mesentery. The transverse and ascending colons were normal. The risks of a major resection were weighed with the findings. It was decided to close the abdomen and try the child on a course of cortisone.

Cortisone therapy was started 10 days post-operatively. The initial dose was 50 mg. a day. At this stage laboratory investigation revealed: Hb, 92%; serum potassium, 4.5 mEq/l.; serum sodium, 135 mEq/l.; serum chloride, 95 mEq/l.; CO_2 combining power, 58 vols.

During the next few weeks the child's condition remained very much the same. The diarrhoea seemed to improve and less blood was found in the stool. There was no gain in weight. The cortisone was then reduced to 37.5 mg. a day. Serum electrolytes remained unchanged.

For the next eight weeks the cortisone was gradually reduced and the child's condition remained very much the same; he, however, had gained 1 lb. (450 g.) in weight and there was no evidence of any oedema.

At the stage where the cortisone was being given in doses of 5 mg. a day the child suddenly developed a pyrexia of 105° F. (40.6° C.) and a pulse of 150. Examination did not reveal any definite cause for this, but the cortisone was discontinued, as some apprehension was felt about the possibility of a perforation of the diseased colon. The temperature continued for five more days and then gradually subsided.

Soon after discontinuing the cortisone the motions again became more frequent and continued to contain blood and mucus. Weight remained stationary, and abdominal examination showed a palpable irregular descending and sigmoid colon. Three months after the start of cortisone the child had not shown any real improvement.

Sigmoidoscopy at this time revealed a red and ulcerated rectum and operation was recommended. Preparation was made for a colon resection, and an intravenous infusion into the long saphenous vein was started on the day of operation.

Operation (D. L. S.).—The incision was made through the old scar. On entering the abdominal cavity thorough search

was made to establish the exact extent of the disease. It was obvious that the descending colon, sigmoid colon, and upper rectum were maximally affected. The rest of the colon appeared to be quite normal. There was no evidence that a small perforation had occurred in the past. The left third of the transverse colon was included in the resection, and this was carried down to the rectum to within 2 cm. above the peritoneal reflexion. An end-to-end anastomosis was performed, the mesenteric opening closed, and the abdomen sutured without drainage.

Micropathology.—There was intense subacute inflammation of the submucosa with areas of ulceration, and mucosal regeneration at the edges of the desquamated areas. Exudate consisted mainly of eosinophil and plasma-cell type. Lymph nodes were the seat of hypertrophy.

Post-operatively the child received 150 ml. of blood and repeated subcutaneous infusions. On the third day he passed two blood-stained motions and his general condition was very satisfactory. Laboratory investigations: Hb, 84%; serum electrolytes normal.

Progress.—Despite slight vomiting, small oral feeds—1 oz. (28 ml.) of milk and 1 oz. (28 ml.) of water—were persisted with; and on the fourth day there was no vomiting, and the feeds were increased to 4 oz. (114 ml.) of milk, 1 oz. (28 ml.) of water, 1 dr. (4 g.) of glucose, and one tablet of sodium citrate four-hourly. By the sixth day the child was on full normal feeds and was having four to six motions a day. No blood or mucus was present. On the twelfth day the wound was well healed, and four days later the child was allowed home. The number of stools has gradually decreased to two a day, with an occasional streak of blood but no mucus. He gained approximately 1 lb. (450 g.) a week for the first two months, and since then the gain has continued steadily. His weight was 29 lb. (13.2 kg.) at the age of 2 years.

Sigmoidoscopy six months after operation showed a red rectal mucosa but no evidence of ulceration; six months later it still showed a congested mucosa but no evidence of ulceration. There has been no blood or mucus in the stool for the past few months.

At the time of writing the patient was very well and able to take all types of food; no restriction has been made in his diet.

Summary

This report deals with a child who at the age of 3 weeks first showed symptoms of ulcerative colitis. Medical treatment proved of no avail. Laparotomy was performed three weeks after admission and a definitive diagnosis of ulcerative colitis involving descending colon, sigmoid colon, and proximal rectum was made. No further operative procedure was undertaken, and a course of cortisone was suggested as a preliminary measure, with the proviso that if this therapy was not effective resection would have to be undertaken.

Three months after cortisone therapy there was no marked improvement, and on the cessation of the cortisone the child's health began to deteriorate rapidly. A resection of the left third of the transverse colon, descending colon, and sigmoid colon, with an end-to-end anastomosis, was performed. The child made an uneventful recovery, and 16 months after operation had gained over 14 lb. (6.4 kg.) in weight and was having two motions a day without any blood or mucus.

We thank Dr. E. Hinden, paediatric consultant, for permission to publish this case.

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CARCINOMA OF THE THYROID FOLLOWING IRRADIATION

BY

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There is now evidence from several sources that irradiation of the thyroid gland in infancy or childhood increases the incidence of cancer of the thyroid in later life. Duffy and Fitzgerald (1950) found that a high proportion of children and adolescents with thyroid carcinoma had been subjected to thymic irradiation in infancy or childhood, and suggested that irradiation might have played a part in the aetiology of these tumours. Simpson *et al.* (1955) reported the results of a survey of 1,400 of 1,722 children who had been treated with *x* rays for thymic enlargement in infancy, and found that the incidence of malignant disease, in particular leukaemia and thyroid carcinoma, was significantly higher in the irradiated children than in their untreated siblings or in the general population. Clark (1955) observed that in 15 cases of thyroid carcinoma in children of 15 years of age or younger there was a history of *x*-ray therapy for benign conditions of the head, neck, or thorax in infancy or childhood. Simpson and Hempelmann (1957) in a later report confirmed their original observations, and suggested that there might be a correlation between the type of irradiation given and the subsequent development of tumours.

In this country Kilpatrick *et al.* (1957) found that three out of eight patients who developed thyroid carcinoma before the age of 35 years had been given ionizing radiation to the neck in childhood. In a later review Wilson *et al.* (1958) report seven patients who developed thyroid carcinoma following irradiation of the neck region. In six of these patients irradiation was given during infancy or childhood. Only one patient developed carcinoma of the thyroid following irradiation of the gland in adult life: this patient, who was treated for thyrotoxicosis by *x*-irradiation at the age of 26, developed an anaplastic carcinoma of the thyroid 37 years later.

It is generally considered that the adult thyroid is not susceptible to radiation cancer. Such a belief has been fostered by an absence in the literature of cases of thyroid carcinoma which might have been attributable to previous irradiation. Negative evidence of an association between radiation and cancer may, however, be misleading. At New End Hospital between 1954 and 1956 three patients who developed carcinoma of the thyroid following irradiation of the neck have been seen: in two of these irradiation was given during adult life.

Case 1

A woman aged 36 was seen in 1955 and found to have a mass in the left lobe of the thyroid gland. In 1937, at the age of 18, she had been treated with *x* rays for thyrotoxicosis. Ten treatments had been given. There were no appreciable radiation changes in the skin or subcutaneous tissues of the neck. Though there was no obvious evidence of hypothyroidism the improvement in her general health when she was subsequently given thyroxine suggested that she had probably been mildly hypothyroid in the first instance. The tumour was removed surgically, and proved on section to be a follicular carcinoma. The interval between irradiation and the diagnosis of cancer was 18 years.

Case 2

A woman aged 49 was seen in 1954. She complained of a goitre which had first been noticed in 1942. In 1916, at the age

of 11, she had been given *x*-ray therapy to the right side of the neck for tuberculous lymphadenitis. She subsequently developed severe radiation dermatitis, and in 1930 an area of skin was excised from the right side of the neck and a skin graft was performed. On examination she was found to have a bilateral nodular goitre which was thought to be non-toxic. There was a skin graft on the right side of the neck extending from the tip of the mastoid process to the clavicle. The incisional scar was keloidal, and the right sternomastoid muscle had become converted into a fibrous cord. A partial thyroidectomy was carried out. Section showed a follicular carcinoma in the right lobe of the thyroid. The interval between irradiation and the diagnosis of cancer was 38 years.

Case 3

A woman aged 69 was seen in 1956 and found to have a firm nodule in the right lobe of the thyroid. In 1915, at the age of 28, she had been given *x*-ray therapy for exophthalmic goitre. Treatment had been given weekly over a period of three years. At the end of this time a remission had occurred. On examination there was slight telangiectasis and atrophy of the skin over the anterior surface of the neck and over the upper part of the sternum. There was no evidence of radiation damage to the subcutaneous tissues. A total thyroidectomy was carried out. Section showed the nodule in the thyroid to be a follicular carcinoma. The interval between irradiation and the diagnosis of cancer was 41 years.

Discussion

X-ray therapy was for many years widely used for the treatment of thyrotoxicosis; it was also often used for treating tuberculous cervical lymphadenitis. As a result a large population has received radiotherapy to the neck for benign conditions. A number of radiation tumours in the deep tissues of the neck have now been reported in the literature. Most of these have occurred in the pharynx (Goolden, 1957), while the thyroid seems to be relatively free from this complication. In addition to the case of Wilson *et al.*, already mentioned, one other instance of radiation cancer of the thyroid after irradiation of the gland in adult life has so far been reported (Kindler, 1943): this occurred in a man of 54 who developed an adenocarcinoma in the left lobe of the thyroid 24 years after *x*-ray treatment for tuberculous glands in the neck.

It is often difficult to decide whether there is a causal relationship between the development of a tumour and previous irradiation. Any tumour which arises in previously irradiated tissue after a suitable latent interval may be suspect, and when several such tumours arise in similar circumstances there is further reason to believe that they may be attributable to irradiation. Further evidence is desirable, however, in order to establish with any certainty a diagnosis of radiation cancer. Although proof is lacking it seems likely that there is an association between radiation and the development of thyroid carcinoma in the cases described above.

It has hitherto been generally accepted that radiation tumours appear only in tissues which have suffered appreciable radiation damage, but there is no real evidence of a threshold dose below which carcinogenesis does not occur. On the contrary, there is evidence from the children who developed malignant disease after irradiation of the thymus that cancer can occur in tissues which have not suffered gross radiation damage. The patients with thyroid carcinoma reported here had varying degrees of damage to the skin and subcutaneous tissues and therefore presumably to the thyroid gland.

The increased incidence of thyroid cancer and leukaemia in children following irradiation, and the increased incidence of leukaemia in patients irradiated for ankylosing spondylitis (Court-Brown and Doll, 1957), were confirmed only after large-scale surveys had been carried out. It would require a survey on similar lines to prove whether or not irradiation of the thyroid gland in adult life increased the incidence of thyroid cancer. In the absence of such a survey it cannot be assumed that the adult thyroid gland is immune to radiation cancer. In the meantime reports of thyroid carcinoma following irradiation would be of interest and might give some indication of whether the adult gland is susceptible to radiation carcinogenesis.

Summary

The literature referring to the increased evidence of thyroid cancer after irradiation of the neck in infancy or childhood is briefly reviewed.

There is at present little evidence to suggest that the adult thyroid is susceptible to radiation cancer.

The development of carcinoma of the thyroid in three patients following irradiation of the neck is reported. Two of the patients received irradiation during adult life. It is considered probable that the tumours in these three patients were induced by radiation, but it is pointed out that it would be necessary to carry out a large-scale survey to find out whether irradiation of the thyroid gland in adult life increased the incidence of thyroid cancer.

I am indebted to Dr. Raymond Greene, Sir Geoffrey Keynes, and Mr. J. E. Piercy for permission to publish these cases.

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Medical Memoranda

Fatal Haematemesis Due to Foreign Body in Stomach

The great majority of swallowed foreign bodies, once having traversed the oesophagus, are passed safely per rectum. Penetration of the stomach wall is a rare event, and the following case report records an instance in which fatal gastric haemorrhage followed ingestion of a piece of chicken bone.

Case Report

A man aged 62 was admitted to the Nuffield Orthopaedic Centre on February 21, 1957, complaining of pain and stiffness of the left hip. He was in excellent health apart from a mild chronic dyspepsia, relieved by antacids, and he had had no previous illnesses. The left hip was found to be severely osteoarthritic. He had a symptomless hypertension of 180/90 and carious teeth, but no other abnormalities were noted on clinical examination.

After dental extraction had been carried out with penicillin cover, he was considered fit for operation on his hip, and a week later a Girdlestone pseudarthrosis was performed on the affected joint.

His immediate post-operative progress was satisfactory, but 24 hours later, shortly after a meal, he vomited food, followed by some altered blood. He improved after a blood transfusion of 2 pints (1,140 ml.), but continued to vomit small amounts of "coffee-ground" fluid. A diagnosis of acute gastric erosion was made.

On the third post-operative day he developed the signs of a very severe bronchopneumonia, which was treated with penicillin and streptomycin. His haematemeses recurred, his general condition deteriorated in spite of continued blood transfusions, and he died on the eighth day.

At necropsy, a chicken-bone 3 cm. long was found impacted at the pylorus. It had penetrated all the coats of the stomach, apart from the serosa, and had eroded a small gastric artery. The stomach and intestine were full of altered blood. There was also a severe inhalation bronchopneumonia.

The patient's hospital menu was then examined, and this showed that chicken had been included in the diet on three occasions, twice after the dental extraction and once the day following the pseudarthrosis. It would seem most probable that the offending bone was swallowed on the last occasion, since this was rapidly followed by vomiting and then a haematemesis.

Comment

Haematemesis due to an ingested foreign body is a rare occurrence. Occasionally the oesophagus is perforated and an adjacent vessel penetrated with fatal consequence, but this occurred in only 3 of the 505 patients treated by Clerf (1940) for foreign bodies impacted in the oesophagus.

In the stomach, haemorrhage may occur from the pressure-ulceration of a bezoar. DeBakey and Ochsner (1938), in a review of the world literature, found 22 such examples in 311 cases. Furthermore, the large collections of metallic objects swallowed by lunatics, criminals, or circus side-show performers may erode the stomach wall and cause bleeding; examples have been recorded by Henderson and Gaston (1938) and by Wheeler (1936). These complications are unusual, but still less common is the haematemesis following laceration of a gastric vessel by a solitary sharp foreign body.

In 1909 Wolfler and Lieblein (quoted by Henderson and Gaston, 1938) reported a fatal gastric haemorrhage from an ingested fish-bone which had perforated the posterior wall of the stomach. Matthews (1930) recorded a fatal haematemesis due to a small piece of copper turning which had ulcerated the oesophagus in three places and which had also transfixed a large vessel on the anterior stomach wall. Dervillée, Lefrou, and L'Épée (1947) described a third case where haematemesis, again fatal, followed impaction of a sharp duralumin ring at the pylorus.

It is perhaps surprising, considering the large number of ingested sharp foreign bodies which are encountered in practice, that they should prove to be such a rare cause of haematemesis.

We thank Mr. R. G. Taylor and Mr. A. Elliot-Smith for permission to publish this case, and Dr. M. S. Dunhill for the necropsy report.

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Intussusception in a Case of Penetrating Abdominal Injury

Exploration of the abdomen for a penetrating injury revealed three interesting lesions—a perforation of the small bowel, an ileo-ileal intussusception, and a very short intestine. It is suggested that this is more than a strange coincidence.

Case Report

The patient, a well-built man of 30, was admitted to the General Hospital, Colombo, with a history of having been stabbed in the abdomen with a knife about three hours previously.

On examination his general condition was satisfactory. His pulse rate was 96, blood pressure 110/75, temperature 98.6° F. (37° C.), and respirations 22. He had an incised wound of his epigastrium with protrusion of omentum through it. The abdomen was not distended, but there was marked guarding and tenderness in the epigastrium below the wound. Bowel sounds were absent. There were no other injuries. He was prepared for urgent laparotomy, and an intravenous drip and gastric suction were begun.

Operation.—Under general anaesthesia a right paramedian incision was made. The prolapsed omentum was withdrawn into the abdominal cavity from within. It was intact. The peritoneal cavity contained a small quantity of blood. A perforation with a diameter of ¼ in. (1.3 cm.) was found in the jejunum, and on further examination of the intestine an ileo-ileal intussusception was located; this was observed for some time, and there was no spontaneous reduction or increase in the mass, which was about 4 in. (10 cm.) long; the sheath was tight at the neck of the intussusception. It was also noticed that the intestine was surprisingly short, and, on measuring, it was found to be about 12 feet (3.6 metres). There was no other injury to the viscera. The perforation in the intestine was closed and oversewn. The intussusception was reduced and there was no bruising or haematoma of the intestine in this region. The stab wound and the paramedian incision were closed in layers without drainage.

Post-operatively, gastric suction and intravenous therapy were continued for 48 hours and penicillin and streptomycin were administered for four days. The patient made an uninterrupted recovery, except for a short delay in the healing of the stab wound, and was discharged on the fifteenth day.

Comment

Intussusception is uncommon in adults, and most cases are secondary to some lesion in the bowel. Intussusception in the absence of a lesion of the bowel is still more uncommon in the adult. Some observers have noted such intussusceptions at necropsy (Boyd, 1955), and others have recorded temporary intussusceptions during abdominal operations (Perrin and Lindsay, 1921). In recent years the occurrence of intussusception in relation to abdominal injury has been recorded in a closed injury of the abdomen (Aldis, 1944). In the case described here it was associated with a penetrating injury. In neither case was there any evidence of injury to the segment involved in the intussusception.

The length of the small intestine, from the ileo-caecal valve to the duodeno-jejunal flexure, was very short, measuring 12 feet (3.6 metres). The average length of the small intestine is about 21 feet (6.5 metres) (*Gray's Anatomy*, 1942). Recent studies show great variations in the length of the small intestine (Underhill, 1955); in the male the range was between 16 and 25 feet (4.9 and 7.6 metres) (measured from pylorus to ileo-caecal valve). Thus in this case the intestine was shorter than the minimum recorded above (allowance being made for the length of the duodenum).

While shortening may have been due to a congenital defect, the simultaneous finding of an intussusception suggests another explanation. Treves was of the opinion that some irregular or disordered contractions of the intestine, perhaps connected with incoordinate action of the circular and longitudinal muscular layers of the bowel, are the prime cause of invagination (Barnard, 1910). Spasm of the longitudinal muscle of the intestine would account for some of the shortening of the bowel. It would also be a factor in the formation of the intussusception. Here, spasm may have been initiated by the intestinal perforation caused by the penetrating injury.

I wish to thank Dr. Noel Bartholomeuz, under whose care this patient was admitted, for permission to publish this case.

H. S. Kirthi Singha, M.B., F.R.C.S.,
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Reviews

HORMONE ASSAY

The Clinical Application of Hormone Assay. By John A. Loraine, M.B., Ph.D.(Ed.), M.R.C.P.(Ed.). Foreword by J. H. Gaddum, Sc.D., F.R.S. (Pp. 368+xii; illustrated. 30s.) Edinburgh and London: E. and S. Livingstone Ltd. 1957.

In an excellent introduction to this timely book Professor J. H. Gaddum prefaces a well-deserved tribute to the recent work of Loraine at Edinburgh by stating that "a few years ago most of the best work in clinical endocrinology was being done in the U.S.A." In my visits to U.S.A. and Canada since 1945 my friends working in this field have gone out of their way to express appreciation of the fundamental quality of the work and research in Britain, so one might consider this parenthetic comment as evidence of mutual appreciation.

The author is concerned not only with the practicability and reliability of assay methods but also with the clinical significance and usefulness of the results obtained. Robert Hutchison tempered scientific curiosity in investigation by urging that the clinician should ask himself beforehand what use, if any, he could make of the evidence he was seeking in the conduct of the case. This pragmatic rule could cut the National Health Service expenses in this field by 90%. Research projects are a different problem, and it can be argued that no one can predict how, when, and where nature will reveal its secrets. The section on the difficult problem of the differentiation and assay of pituitary gonadotrophins is of high quality, but its clinical applicability frugal. Pregnancy tests and assays of chorionic gonadotrophins are lucidly described and their diagnostic applications clearly indicated. The most sensitive method for assaying thyrotrophin is shown to depend on the radioactive-iodine uptake and discharge in chicks, guinea-pigs, and mice. Abnormally high T.S.H. levels have been reported in myxoedema and acromegaly, but this assay is usually of more scientific than practical interest.

The ability of the author to deal concisely and accurately with an abstruse field is well illustrated in the adrenotrophin section, which covers the chemical nature of corticotrophin, the corticotrophin factors differentiated by methods of assay, the separation of the melanophore-expanding hormone, and the biological methods of assay of blood corticotrophin concentration in man. It is in keeping with biological expectation that blood corticotrophin should be raised in Addison's disease, after total adrenalectomy, and in congenital adrenal hyperplasia, but the failure of many observers to find raised corticotrophin values in Cushing's syndrome brings the problem of aetiology in line with the equally complex one of thyrotoxicosis aetiology. Perhaps the author will add a chapter to the next edition reviewing the interrelationship of hormone assays and interpretation over the entire endocrine field. The section on growth hormone assay might integrate the work of Randle on the indirect method of assay by diaphragmatic glucose uptake, referred to in the later insulin section. Both for oestrogens and androgens, the author accepts modern practice of chemical methods. Unfortunately 17-ketosteroid assays are insensitive and often misleading in clinical medicine. The corticosteroid chapter in itself makes the book a good acquisition; and I am inclined to agree with the view that "it is probable that in the future assay methods for corticosteroids in body fluids will depend either on paper chromatographic techniques or on procedures employing radioactive steroids."

S. LEONARD SIMPSON.

DOCTORS IN A SICK SOCIETY

The Matrix of Medicine. Some Social Aspects of Medical Practice. Edited by Nicolas Malleson, M.D., M.R.C.P. (Pp. 234+xviii; illustrated. 45s.) London: Pitman Medical Publishing Company, Ltd. 1958.

"Medicine and social medicine are but part and parcel of each other," writes Dr. Malleson in his introduction to this book, and he has asked his contributors to illustrate this theme. The sickness of any individual must surely affect the community in some degree, and to this extent all illness has its social aspects; it is not true, however, that all disease springs from social causes. The three clinicians, therefore, writing in this book on the climacteric, Dr. Brian Kirman writing of mental deficiency, and Dr. Richard Asher in his thoughtful and entertaining chapter on somatopsychics, naturally produce little evidence that the disorders they are considering spring from the social environment. These particular essays illustrate the important, but unintended, conclusion that social medicine—human ecology—by no means comprehends the whole of medicine.

Some of the other contributors are able to give Dr. Malleson's hypothesis much better support. They show in a striking fashion that the rapid changes which are occurring in man's social environment are producing disorders which demand a different approach from the doctor. Dr. Robert Logan, in a remarkable and realistic essay on industrial medicine, critically examines the five duties of the industrial medical officer as laid down by the B.M.A.; and he finds that the industrial doctor's most important functions lie outside these prescribed duties. He stresses particularly the value of his "non-directive counselling" in the prevention and cure of factory malaise. Dr. Malleson himself reaches the same conclusion as to the most valuable work of the doctor in the student health service, his chief objective being "the efficient and harmonious adjustment" of the student to university life. Both Dr. Malleson and Dr. Logan are critical of the value of the routine medical examination. Dr. J. C. G. Evans, a family doctor, in a splendid little essay, writes of himself as the counsellor in the home, as are these other doctors in the factory and the university. He sees, too, that, while diagnostic medicine still lies largely within the hospital, therapeutic medicine is slowly returning to the family doctor.

Of the other contributors, Drs. Lightwood and Brimblecombe tell of the interesting St. Mary's Hospital experiment of taking the young paediatricians and the medical students into the home to collaborate with the family doctor in the care of sick children; Dr. Marjory Warren writes wisely of the social aspect of geriatrics; Dr. Cicely Williams widely surveys malnutrition as a world problem, and Dr. Horace Joules writes as if his trumpet-blast must blow away all the cigarette and coal smoke—these foolish things—from our stupid world.

Dr. Malleson has done well to compile this interesting, if unequal, book. The editor of such a collection of essays has to see his purpose clearly and give each member of his team a strict assignment if the book is to reach a uniform standard of excellence. Dr. Malleson hardly seems to notice that one of his riders has cantered briskly in a direction exactly opposite to his instructions. It is a pity that the ridiculous price of this book—45s. for 234 pages and no index—ensures that it may be borrowed but will not be bought.

D. V. HUBBLE.

PSYCHO-ANALYSIS AND CONTEMPORARY THOUGHT

Psycho-analysis and Contemporary Thought. By D. W. Winnicott, John Bowlby, Ilse Hellman, Marion Milner, Roger Money-Kyrle, Elliott Jacques, and Joan Riviere. With an introduction by Sylvia Payne. Edited by John D. Sutherland. (Pp. 149; illustrated. 25s.) London: Hogarth Press, 1958.

Every now and then psycho-analytic societies, being sensible of the fact that the body of Freudian theory to which they have fallen heir is as relevant to man's social and cultural activities as to his mental disorders, arrange a series of lectures intended to inform the intelligent public on psycho-analytic views concerning such matters as the origins of social morality, child-rearing, pedagogy, art, philosophy, and even economics. In the past the success of such ventures has depended partly on the contributors' capacity to present unfamiliar ideas on familiar subjects in a digestible form, and partly on their grasp, not just of psycho-analytic principles, but of the particular subject to which they have chosen to apply psycho-analytical measures. Judged by

these standards the present book of essays falls considerably short of what the public is entitled to expect of those who embark on popular exposition. Exceptionally, there is an extremely good and unassuming essay on the psycho-analytic principles of child guidance by Dr. Bowlby, and a useful if slightly more diffuse runner-up on pedagogy by Ilse Hellman. Of the other contributions it must regretfully be said that they are much too disjointed in form and that the correlations attempted between unconscious and conscious factors fall between two stools, being either so speculative or so involved as to alienate or confuse the average receptive reader. In some cases, as in Dr. Jacques's essay on the current economic crisis, these drawbacks are accentuated by a naivety of approach that borders on the jejune. In any case, the title of the book is misleading; for, apart from one or two references in Mrs. Milner's essay on art, its contact with contemporary thought is extremely exiguous, even where, as in Money-Kyrle's essay on philosophy, a close contact might have been anticipated. More disappointing, however, than the sparsity of new and stimulating formulations is the absence of clear thinking and clear writing. In short, from the point of view of disciplined exposition the book is scarcely worthy of inclusion in the International Psycho-analytical Library series, which, with but a few outstanding exceptions, has maintained consistently high scientific and literary standards.

EDWARD GLOVER.

PHARMACOLOGY AND THERAPEUTICS

The Pharmacologic Principles of Medical Practice. A Textbook on Pharmacology and Therapeutics. By John C. Krantz, Jr., and C. Jelleff Carr. Fourth edition. (Pp. 1,313 +xi; illustrated. £5 12s.) London: Baillière, Tindall and Cox, Ltd. 1958.

The title of this book indicates that the authors intend it to be used by doctors in practice. The book does not, however, answer the questions to which doctors in practice are most likely to want the answers. These are of two kinds. The first is, What are the advantages and disadvantages of this particular analgesic or that particular antibiotic? The second is, What are the different ways in which a particular disease, such as Parkinsonism, can be treated?

This book is, in fact, a book for students rather than for those in practice, and it follows the lines of many courses in pharmacology. It relies very heavily on American sources for its information, and, since many of the more interesting discoveries in this field have been made in Europe, the story of the introduction of many new agents, which often sheds a great deal of light on their proper use, is scarcely indicated.

Even for students the book does not sufficiently select and underline the best remedies. Thus, for the treatment of roundworm infestation oil of chenopodium and santonin are described before piperazine is mentioned. To-day the use of piperazine should displace that of oil of chenopodium and of santonin altogether, and the authors surely fail in their duty in not making this clear.

For the student, again, the book is too large. No student given the time allotted to pharmacology in most American medical schools is likely to be fired with enthusiasm when he has to wade through so much dull matter. The art of writing the short book has yet to be developed. However, here and there pages of great interest are to be found, as those in which Banting's account of his discovery of insulin is given.

J. H. BURN.

PAEDIATRIC MANAGEMENT

Pediatric Index. A Guide to Symptomatological Diagnosis and Current Management. By Edwin F. Patton, M.D. (Pp. 639. £5 1s. 6d.) London: Henry Kimpton. 1958.

When Wilburt Davison produced *The Compleat Pediatrician* in 1919 it was greeted with a certain amount of amusement and a great deal of criticism. However, it survived, and, indeed, flourished. A rewritten seventh edition appeared last year, and there are many thousands of doctors and students who are grateful to Dr. Davison for his masterpiece.

Now a *Pediatric Index* has appeared, rather more grandiose in form and ambition, for the author says it is intended "to assist in providing the best possible care to any child with any problem" and that "it should be particularly useful to general practitioners, students, and less experienced pediatricians," but "even pediatric 'ivory towers' may be helped in running down obscure diagnoses." The book is in two main sections, the first consisting of a series of alphabetically arranged signs and symptoms, and the second aiming to supply "definitive diagnoses and current management." It is well produced and remarkably free from typographical errors, but it is maddening in its multiplicity of cross-references, and it takes a long time to "run down" even a simple diagnosis—indeed, so long that it is not really worth while, and, when achieved, the treatment recommended is often too sketchy to be of any practical value.

WILFRID GAISFORD.

INTRODUCTION TO SURGERY

An Introduction to Surgery. Edited by David H. Patey, M.S.(Lond.), F.R.C.S.(Eng.). (Pp. 228+xi; illustrated. 17s. 6d.; student's edition 9s. 6d.) London: Lloyd-Luke (Medical Books) Ltd. 1958.

This useful little book is meant
For those on surgery intent,
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The Physical Treatment of Varicose Ulcers, by R. Rowden Foote (pp. 126, illustrated; E. and S. Livingstone Ltd.: 15s.), describes the essentials of massage and exercises for use by the physiotherapist and nurse attached to the varicose clinic. A description of the common types of leg ulcers is given, and reference is also made to surgical treatment.

The Sherrington Lectures delivered by Lord Cohen of Birkenhead at the University of Liverpool in 1955 have now been published (*Sherrington: Physiologist, Philosopher and Poet*; 108 pp., Liverpool University Press, 17s. 6d.). The first lecture is a brief but admirable sketch of Sherrington's life. The two remaining lectures deal with Sherrington's physiological work and with his philosophical and poetical writings. Three portraits and a bibliography of his published writings are included, and the whole provides a masterly assessment of the life and work of "the most profound student of the nervous system the world has yet known."

The Medical Research Council's Memorandum No. 36, *The Determination of the ABO and Rh(D) Blood Groups for Transfusion*, which has recently been issued by H.M. Stationery Office (pp. 46; 3s. 6d.), is a revision of War Memorandum No. 9, published in 1943. The great and increasing frequency with which transfusions have been given, and the rapid advance of research on the subject, have led to a fuller appreciation of the errors that may occur in blood grouping and direct-matching tests and to the elaboration of methods designed to avoid such errors. These considerations have made it necessary to rewrite almost the entire text. The section on the Rh factor has been considerably expanded and some new sections have been added. The revision has been carried out by a Working Party specially appointed for the purpose.

At the time of his death in 1956 the late H. Willoughby Lyle had completed the manuscript of *Applied Physiology of the Eye*, and this has now been revised by T. Keith Lyle and published by Baillière, Tindall and Cox (pp. 341, illustrated; 45s.). It gives the main facts relating to the physiology of the eye and the organs which have a direct or indirect physiological connexion with the function of vision. It is designed particularly for those working for higher examinations in ophthalmology and for practising ophthalmologists who wish to have an up-to-date account of the physiological aspects of ophthalmology.

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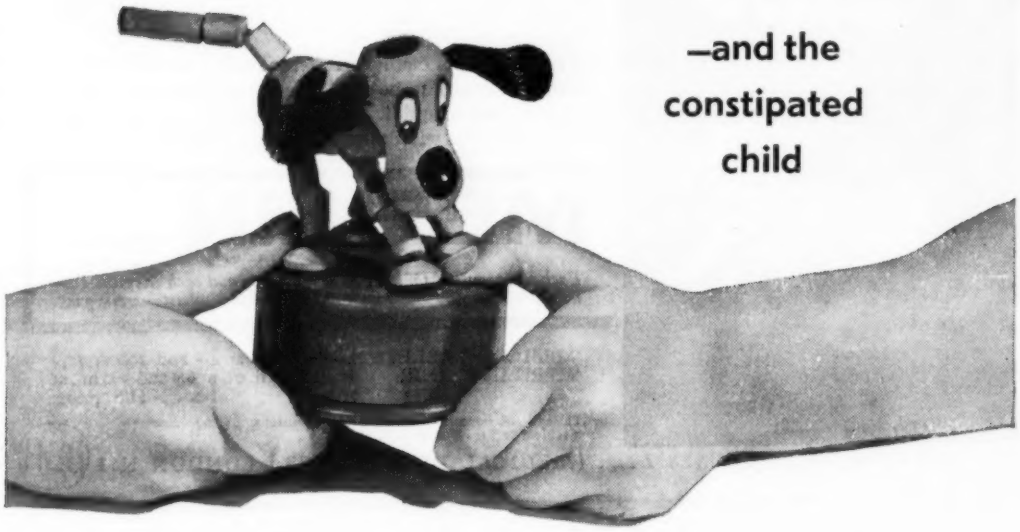

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BLOOD GROUPS IN CYPRUS AND THE NEAR EAST

Populations which within recent millenniums have shared a common ancestry have, it is generally accepted, similar blood-group frequencies. Hence a difference in blood-group frequencies is evidence that ancestries differ, at least in part, or that the processes of evolution have altered the frequencies in at least one of the populations under consideration. The converse argument cannot be applied so simply, for a similarity in blood groups may be accidental, if tests for only one blood-group system have been performed. But many genetically independent blood-group systems are now known, and, if the frequencies of the blood groups of several systems show close resemblances in two populations, this may be taken as evidence of consanguinity. Similar considerations apply to all other genetical systems which include two or more relatively common allelomorphic genes, such as those for the haemoglobins, the haptoglobins, and the ability to taste phenylthiocarbamide.

The study of blood groups and other genetic evidence thus provides a firm foundation in anthropology, and such studies have shown, what was indeed known from other evidence, that nearly all human populations are complex mixtures. The difficulty of using blood-group investigations in the study of their ancestry and relationships does not arise from any doubt about the fundamental principles, but from the great complexity of the problems to which those principles must be applied. Another difficulty is the lack of data, especially for systems other than the ABO. While data have been published on the ABO groups of nearly 6,000,000 people, information is available on the Rh and MN groups for only, very roughly, 100,000, and for all the other systems the numbers are much smaller. Thus, in many of the problems that arise study must be confined to the ABO groups. It is instructive to consider as an example the distribution of these groups in the British Isles. The frequency of group O is considerably higher in Scotland, Wales, and Ireland than in England, and southern England in fact shows a closer resemblance to northern France than to Scotland in its blood-group frequencies. The distribution of the ABO groups in the whole of north-western Europe is now known in some detail, and it may soon be possible to analyse the modern population in terms of a small number of basic populations, and perhaps to identify these historically.

With a few notable exceptions our knowledge of the blood groups of the rest of Europe and the world is much less detailed: the eastern Mediterranean area with its diverse modern populations and its rich historical and archaeological records presents a particular challenge, and two contributions on this subject in the *Journal* this week are therefore especially welcome.

The detailed work of Dr. A. E. Mourant and his colleagues (p. 937) on the Turks and Eti-Turks will yield its full value only when similarly detailed studies have been made of the varied populations of the Levant to the south. The Rh and MN groups show a general relation to Europe, but, on the basis of this and other investigations, the ABO groups, probably a more sensitive indicator of the history of the last one or two thousand years, show a hiatus between the inhabitants of the Greek peninsula and islands, with high O and low A frequencies, and those of Asia Minor, with much lower O and higher A frequencies. In Syria and Lebanon the very varied peoples show a correspondingly varied picture of the ABO blood groups, with a general resemblance to Turkey rather than to Greece, but mostly with a higher B frequency than in either of those countries. Nothing is known of the Rh groups in this area.

Dr. P. A. Clearkin (p. 939) has examined the distribution of ABO and Rh blood groups in Cyprus, both in Greek-speaking and in Turkish-speaking Cypriots. Basing his conclusions on fully adequate population samples, he finds but little difference between the two linguistic divisions as regards either their ABO or their Rh (D) groups. In their ABO frequencies, however, both divisions of the Cypriot population differ widely from the European Greeks, and much more closely resemble the Turks and the peoples of the Levant. The differences between Cypriots and Greeks in ABO frequencies, and incidentally also in Rh frequencies, are evidence of a racial difference, though the slightly lower frequency of B in Greek- than in Turkish-speaking Cypriots could perhaps be regarded as pointing to a small amount of Greek ancestry. But the resemblance to Turkey in ABO frequencies is not accompanied by a resemblance in Rh frequencies, for while the Turks and Eti-Turks of the Mersin area, for whom alone data are available, have about 10% of Rh-negative people, Greek-speaking and Turkish-speaking Cypriots have only 2.5 and 3.2% respectively, values which are below any others known in the

Mediterranean basin. It is possible that these figures could be matched somewhere in the Levant.

The conclusion is therefore clear that there is, so far as blood groups show, no detectable racial difference between the two linguistic classes of Cypriots, but that both differ widely from the European Greeks, and also differ, though less distinctly, from the Turks. How far this is relevant to possible solutions of the present political problem is not so clear. If we can imagine a redrawing of boundaries in north-western Europe on the basis of blood-group frequencies, this would reunite populations which were of common ancestry and so satisfy one or two minority aspirations, but its main effect would be to separate populations which had been under common peaceful government for centuries, and bring together groups of people with neither language nor political sympathies in common. Blood groups are one of the very many factors which ought to be known and considered by the statesmen trying to bring peace to Cyprus. They may not be a major factor politically there, but they do conclusively disprove some claims to racial kinship that have been made. They should show both "Greeks" and "Turks" in Cyprus, when a calm examination of the problem becomes possible, that they have something in common which should transcend their differences—a common ancestry as well as a common humanity.

FLAPPING TREMOR

Various neurological abnormalities may occur in cases of severe liver disease, and in 1949 R. D. Adams and J. M. Foley[1] recognized a particular type of tremor of the outstretched hands to which they subsequently[2] gave the name "asterixis," which means inability to maintain a fixed posture. The sign is elicited by having the patient stretch out his arms with the hands dorsiflexed. In less than a minute, sudden flexion-extension movements appear at the wrist so that the hand itself jerks up and down. Each up-and-down movement lasts only a fraction of a second, but little bursts of such movements usually occur, out of phase in the two hands, giving a vivid impression to the observer and accounting for the usual term, "flapping tremor." As it has commonly been regarded as diagnostic of advanced liver disease, the term "liver flap" has also been used.

It is a common finding in advanced liver disease and especially in hepatic precoma. Apart from coma, the neurological and psychological disturbances due to chronic liver disease are manifold, and Sheila Sherlock and her colleagues have given an excellent description of them in 17 patients with chronic liver disease who presented with intermittent neuropsychiatric disturbances which they had suffered for six months to six years.[3] In these patients flapping tremor was invariably present at some stage, and it constituted the main neurological abnormality in nine of them. The degree of liver failure was not necessarily severe, but an extensive portal-systemic collateral circulation was present in the majority. This suggested the absorption of a toxic nitrogenous substance, or substances, from the intestine which reached the systemic veins through the collateral channels in sufficient quantities to cause cerebral disturbance. An increase in dietary protein, or administration by mouth of ammonium chloride or methionine, can cause exacerbations in this type of patient, with corresponding changes in the electroencephalogram.[3-5] Recently chlorothiazide has been shown to induce the syndrome in some patients with cirrhosis of the liver.[6]

After Adams and Foley published their observations it began to be appreciated that flapping tremor might occasionally occur in non-hepatic disease, such as cor pulmonale, the malabsorption syndrome, hypomagnesaemia, and uraemia.[7-10] A valuable contribution to the subject has now been made by H. O. Conn,[11] who describes six further examples of flapping tremor occurring in chronic pulmonary disease with cardiac decompensation. After remarking that cor pulmonale is in fact the non-hepatic disease in which asterixis most commonly occurs, Conn proceeds to an excellent discussion of the theories which have been advanced to account for the phenomenon. First, as to the possibility of liver disease in the pulmonary cases observed by him, he concludes that severe liver disease was not responsible for asterixis in these patients, "although it is impossible to exclude subtle hepatic abnormalities." Secondly, as to raised ammonia levels in the blood being the common factor responsible for the tremor, he quotes work which shows poor correlation between these levels and the occurrence of hepatic coma. Moreover, the admini-

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[9] Hammarsten, J. F., and Smith, W. O., ibid., 1957, **256**, 897.
[10] Smythe, C. M., and Baroody, N. B., *J. Amer. med. Ass.*, 1957, **165**, 31.
[11] Conn, H. O., *New Engl. J. Med.*, 1958, **259**, 564.

stration of ammonium compounds to several of the patients with pulmonary disease had no influence on the asterixis. Thirdly, though flapping tremor can certainly occur in cases of magnesium deficiency,[9] there is no reason to regard this as the common factor in the various clinical states in which asterixis may appear. Fourthly, a number of other metabolic disturbances, such as acidosis, alkalosis, hypoglycaemia, sodium depletion, and potassium depletion, can be ruled out as unlikely to be the essential factor in the condition.

Cerebral hypoxia is possibly the disturbance which is common to all these patients with asterixis. In some of them, as, for example, those with cor pulmonale, the oxygenation of the blood is defective. Metabolic disturbances such as occur in liver failure and uraemia might produce the same effect on the brain through interference with enzyme activity, and Conn cites evidence to show that the E.E.G. "coma pattern" met with in severe hepatic disease is also found in patients with asterixis owing to pulmonary insufficiency or uraemia. He therefore tentatively suggests that a variety of metabolic or mechanical disturbances are capable of interfering with the basic oxidative processes of cerebral metabolism, and he adds:

"Inherent in this hypothesis is the prediction that asterixis will be observed in a series of additional diseases in which cerebral metabolism is depressed. Such diseases as severe anemia, diabetic acidosis, hypoglycemia, barbiturate intoxication, congestive heart failure and even senility fall into this category."

In any event, whatever may be the true explanation of the phenomenon of asterixis, it is evident that this sign cannot be regarded as diagnostic of liver disease. For this reason the term "liver flap" should be discarded and asterixis (or the more colloquial and descriptive "flapping tremor") be preferred.

CARCINOGENIC RISK OF THYROID IRRADIATION

It has long been recognized that the thyroid gland is radio-resistant. In the treatment of malignant disease of the neck and upper thorax the thyroid is frequently submitted to heavy doses of *x* and gamma rays without clinically appreciable impairment of function, immediate or remote. It is only within the last decade or so that the possibility of the late development of carcinoma after thyroid irradiation has been seriously considered. In 1949 E. H. Quimby and S. C. Werner[1] investigated the subsequent history of several hundred patients who had been submitted to deep *x*-ray therapy for hyperthyroidism by questionary addressed to radiologists and thyroid specialists. Not more than three cases of cancer of the thyroid were reported that they considered could have been attributable to radiation. In 1950 B. J. Duffy and P. J. Fitzgerald[2] reported a high incidence of previous exposure to ionizing radiation in young patients with thyroid carcinoma. In 1955 C. L. Simpson and colleagues[3] showed that the incidence of carcinoma of the thyroid in children and young adults who had been given from 200 to 600 r to the neck and chest in infancy for thymic enlargement is significantly higher than in untreated siblings and the general population; and in 1957 Simpson and Hempelmann[4] investigated 1,502 patients whose necks had been irradiated in childhood, and found 10 cases of thyroid carcinoma and 7 of thyroid adenoma. In a comparable series of unirradiated patients there was no case of carcinoma and one of adenoma. Similar observations were made by D. E. Clark[5] and G. H. Fetterman.[6]

In an important communication in the opening pages of the *Journal* this week Professor G. M. Wilson and his colleagues record 9 further cases of the formation of thyroid tumours following irradiation, 7 of them carcinoma and 2 adenoma. Of the patients who developed carcinoma, 4 had had *x*- or gamma radiation applied to the neck under the age of 1 year, and in 2 others the radiation was first applied to the neck at the ages of 12 and 14 years respectively. In the seventh case the neck was irradiated at the age of 26 years. In all cases the radiation had been applied originally for simple non-malignant conditions such as naevus, keloid, and in one case eczema. The estimated radiation dose to the thyroid varied widely. The lowest total dose was 130 r and this was in the youngest child, who was aged 2 months at the time of irradiation. The highest total dose was 2,700 r to a child of 13. The latent period between the application of the last dose of radiation and the development of the carcinoma varied from 5 to 18 years.

The conclusion seems inescapable that irradiation of the thyroid in child and early adult life may lead to the late development of carcinoma in that organ, although, as Wilson and his colleagues point out, the

[1] Quimby, E. H., and Werner, S. C., *J. Amer. med. Ass.*, 1949, **140**, 1046.
[2] Duffy, B. J., and Fitzgerald, P. J., *Cancer*, 1950, **3**, 1018.
[3] Simpson, C. L., Hempelmann, L. H., and Fuller, L. M., *Radiology*, 1955 **64**, 840.
[4] —— —— *Cancer*, 1957, **10**, 42.
[5] Clark, D. E., *J. Amer. med. Ass.*, 1955, **159**, 1007.
[6] Fetterman, G. H., *Amer. J. Dis. Child.*, 1956, **92**, 581.
[7] *Hazards to Man of Nuclear and Allied Radiations*, Medical Research Council, Cmd. 9780, H.M.S.O., 1956.
[8] Dobyn, B. M., Vickery, A. L., Maloof, F., and Chapman, E. M., *J. clin. Endocr.*, 1953, **13**, 548.
[9] Freedberg, A. G., Kurland, G. S., and Blumbart, H. L., ibid., 1952, **12**, 1315.

risk to any individual as a result of exposure is small. It is likely that the hazard exists over the whole range of useful therapeutic dosage and possibly even with the dosage of radioactive ^{131}I normally given in tests of thyroid function.

In adult life it is generally considered to be unlikely that irradiation of the thyroid leads to the development of carcinoma, but this week Dr. A. W. G. Goolden reports (p. 954) two cases which indicate that this question is worth further study. His Case 1 is a woman who was irradiated for thyrotoxicosis at the age of 18 and found to have carcinoma of the thyroid at 36. In his Case 3 he reports the finding of thyroid carcinoma in a woman aged 69 who had received *x*-ray therapy when aged 28. The extent to which such associations between irradiation in the adult and the subsequent development of thyroid cancer are causative evidently needs further study. Goolden considers that "although proof is lacking it seems likely that there is an association between radiation and the development of thyroid carcinoma" in his cases, and many would agree with his view that "reports of thyroid carcinoma following irradiation would be of interest and might give some indication of whether the adult gland is susceptible to radiation carcinogenesis."

Conclusions based on previous experience of thyroid irradiation must necessarily refer to external irradiation by *x* rays or radium. But, since the latent period for the development of carcinoma following irradiation in adult life is probably at least 20 years,[7] no conclusions can yet be based on any series of patients who have received radioactive iodine, since it is only about 16 years since this isotope has been in clinical use for test investigations. Theoretically, owing to the wide variation in the radiation dosage from the absorbed isotope sustained by the thyroid cells at different points, it is certain that some cells surviving damage will have been irradiated with a dose which in other tissues is known to lead to tumour formation. Indeed, B. M. Dobyn and his co-workers[8] and A. G. Freedberg and his co-workers[9] have described nuclear changes in treated human thyroids which are suggestive of premalignant change. The risk of the late development of carcinoma in children in particular makes it justifiable only in exceptional circumstances to use radioactive iodine even for test purposes, or to use *x* rays or radium in the neighbourhood of the thyroid in the treatment of simple conditions such as thymic enlargement, naevi, and keloid scars. In later adult life the risk of carcinoma would seem to be a factor of less importance, but further study of it is urgently needed.

VIRUS DISEASES IN PREGNANCY

What are the chances of a woman bearing a malformed child if she has had an attack of rubella or one of the other virus diseases during pregnancy? This is a question which many workers have tried to answer since N. M. Gregg[1] first showed in Australia that rubella early in pregnancy can be associated with malformations in the foetus. The characteristic abnormalities are cataract, deafness, mental deficiency with or without microcephaly, and congenital heart disease, usually ventricular septal defect or patent ductus arteriosus. In 1943 C. Swan and colleagues[2] suggested that women who contracted rubella during the first two months of pregnancy would nearly all have children with malformations, and that rubella in the third month would result in about 50% of the children being affected. This estimate was based mainly on a retrospective survey in which children with defects were observed, and then a history of the health of the mother during the pregnancy obtained. Investigations of this type omit the normal children whose mothers have had rubella, and no assessment of the risk to the foetus can be based on them. Even so, rubella in early pregnancy has been regarded as an indication for therapeutic abortion.[3] For instance, M. Greenberg and colleagues[4] studied 103 women in New York who between 1949 and 1955 had had rubella during the first trimester of pregnancy, and found that 43.7% of them had had therapeutic abortions performed because of the rubella.

The risk run at the different stages of pregnancy can best be estimated from a prospective method of inquiry in which the illness in the pregnant woman is first observed and diagnosed, and the condition of the child born to her subsequently noted. In 1951 the desiderata for the ideal inquiry were well stated by W. P. D. Logan,[5] but the number of cases of rubella which occur during pregnancy is so small that no single series yet reported has been large enough to provide accurate estimates. Greenberg and colleagues[4] combined all the nine prospective series published up to 1957, and found that out of a total of 125 children born of women who had had rubella during the first trimester only 12% had congenital malformations. But these data may have been disproportionately weighted with cases in which infection occurred towards the end of the first trimester of pregnancy, because therapeutic abortion may have been carried out mainly for those women infected in the first two months.

Recently A. Bradford Hill and colleagues[6] have reported the results of a prospective inquiry, in which the children born of nearly all the affected mothers were

[1] Gregg, N. M., *Trans. ophthal. Soc. Aust.*, 1941, **3**, 35.
[2] Swan, C., Tostevin, A. L., Mayo, H., and Black, G. H. B., *Med. J. Aust.*, 1943, **2**, 201.
[3] Wesselhoeft, C., *New Engl. J. Med.*, 1949, **240**, 258.
[4] Greenberg, M., Pellitteri, O., and Barton, J., *J. Amer. med. Ass.*, 1957, **165**, 675.
[5] Logan, W. P. D., *Brit. med. J.*, 1951, **2**, 641.
[6] Hill, A. B., Doll, R., Galloway, T. McI., and Hughes, J. P. W., *Brit. J. prev. soc. Med.*, 1958, **12**, 1.
[7] Brown, C. M., and Nathan, B. J., *Lancet*, 1954, **1**, 975.
[8] Brawner, D. L., *J. med. Ass. Ga.*, 1955, **44**, 451.
[9] Pitt, D. B., *Med. J. Aust.*, 1957, **1**, 233.
[10] Lamy, M., and Seror, M. E., *Sem. méd. prof. méd.-soc.*, 1956, **32**, 1085.
[11] Grönvall, H., and Selander, P., *Nord. Med.*, 1948, **37**, 409.
[12] Krugman, S., and Ward, R., *New Engl. J. Med.*, 1958, **259**, 16.

subsequently examined, and the data are published in sufficient detail for a separate estimate to be made of the risk for each month of pregnancy. Of the seven women having rubella during the first four weeks of pregnancy, three had babies with the characteristic abnormalities, and of the eighteen with the illness during the first trimester four and possibly five had affected babies. The authors combined their results with those of three other investigations[7–9] in which a prospective method of inquiry had been strictly applied and the data published for each month of pregnancy. In the four series there are fifty women who had rubella during the first twelve weeks, and the results show that the risk of abnormality may be as high as 50% when the infection occurs in the first month of "pregnancy" (that is, in the four weeks following the start of the last preceding menstrual period). Subsequently, as the length of time between the last menstrual period and the appearance of the disease increases, the risk of abnormality steadily decreases. In the second month the risk was 25%, and it is possible that no defects were due to the maternal illness when it occurred after the thirteenth week of pregnancy. A fifth inquiry,[10] carried out in France, was not combined with these four because its results are so different, suggesting that the risk during both the first and second month of pregnancy may be over 80%. Bradford Hill and colleagues concluded that it is unlikely that the great differences in the results obtained by different groups of workers can be explained by the operation of chance and by differences in the methods of inquiry. It is possible that the effect of a maternal attack of rubella may vary at different times and in different localities.

The high risk during the first four weeks of pregnancy revealed by the research of Bradford Hill and his colleagues is of importance when considering means of preventing maternal rubella. Keeping pregnant women away from cases of the disease is practised, and for pregnant women who have been exposed to infection S. Krugman and R. Ward[12] have recommended the early administration of large doses of gamma globulin. Neither of these measures may be very effective in preventing foetal malformations if the highest risk is when rubella occurs before pregnancy is even suspected. It is thus not surprising that some physicians advocate the deliberate exposure of young girls to the disease to prevent their catching it in the early stages of pregnancy.

As well as investigating the effects of maternal rubella, Bradford Hill and his colleagues examined the children of women who had measles, chicken-pox, and mumps during pregnancy and found no evidence of the production of congenital malformations by these other virus diseases. This result is in agreement with the great majority of previous investigations, including that of H. Grönvall and P. Selander,[11] who, in addition, found no characteristic effects from infective hepatitis, poliomyelitis, herpes zoster, and scarlet fever.

The doctor who has to advise a woman on the risk of her baby being affected when she has had a virus disease during pregnancy can reassure her if the disease has been anything other than rubella. Even rubella is apparently unlikely to affect the foetus if it has occurred after the thirteenth week. When it has occurred during the first four weeks, however, the recent data suggest that the risk of serious malformation may be nearly 50%.

METABOLISM OF LIPIDS

The September issue of the *British Medical Bulletin*[1] presents a group of valuable reviews on several of the most important aspects of lipid metabolism. The application of new methods of chyle collection, the introduction of isotopic labelling techniques, the detailed study of the behaviour of different types of lipid molecule, and more detailed understanding of certain complex enzymological processes have all enabled us to advance our knowledge of lipid metabolism.

The first step in the transport of exogenous lipid is absorption from the intestine, and A. C. Frazer reviews the mechanism of fat absorption according to information obtained from the study of certain malabsorption states. J. Glover and R. A. Morton emphasize that the acceptance by proteins of individual sterols shows high structural specificity, which cannot be accounted for in terms of simple absorption. Exchange of sterols occurs between a mucoprotein complex in the intestinal villi and the cell membrane, and transport within the cell is effected by a series of transfers to and from lipoproteins. Lipoproteins allow the transport of lipids in the blood stream, and J. E. French, B. Morris, and D. S. Robinson consider the mechanisms for the removal of lipoproteins, chylomicra, and unesterified fatty acids from the blood. Capillary permeability is important for the removal of lipoproteins and chylomicra, and the latter may also be removed from the blood by some enzyme with a hydrolytic action analogous to the heparin-clearing reaction. Hormones also influence the lipoproteins in the blood. G. S. Boyd and M. F. Oliver point out that no conclusions can yet be reached on the precise action of any given hormone, since hormones can alter the concentration of lipoproteins in the blood by numerous pathways; these include cholesterol absorption, hepatic cholesterol biosynthesis and degradation, and the interchange of lipoproteins between the plasma and interstitial fluid. B. Bronte-Stewart continues this consideration of blood lipids by reviewing the effect of the administration of various dietary fats. While pointing out that assumption rather than fact underlies the hypothesis that ischaemic heart disease results from a disturbance in fat metabolism, he stresses that of all the environmental variables no other at present known can be so closely related to the pathological, metabolic, and epidemiological features of the disease as the nature of the dietary fat intake.

One of the current problems in the understanding of the aetiology of atherosclerosis is the importance of thrombosis. J. C. F. Poole describes the influence of certain lipids on blood clotting and concludes that ethanolamine phosphatide is an essential substance for blood coagulation. However, not enough is known about the connexion between clotting and thrombosis

[1] *Brit. med. Bull.*, 1958, **14**, 197–278.

to decide whether or not the part played by fats in coagulation is relevant to the mechanism of thrombosis. H. M. Sinclair considers the structural function of essential fatty acids, particularly in relation to the skin. A. T. James and J. E. Lovelock describe analytical studies of essential fatty acids in coronary disease and idiopathic hypercalcaemia of infancy; they conclude that there is little satisfactory evidence for a deficiency of essential fatty acids in either condition, and believe that it has yet to be proved that any human disease is due to such a deficiency. Other stimulating reviews of the biosynthesis of fatty acids and of cholesterol, of the hormonal influences of *in vitro* lipogenesis in mammary tissue, and of the structure of lipids and myelin should make this issue of the *British Medical Bulletin* attractive to many readers with diverse interests.

NUFFIELD BOUNTY

In the first 15 years of its existence the Nuffield Foundation has given away about £8½m. Of this, £6½m. has been spent in the United Kingdom and £2m. in the Commonwealth. The latest report to be published[1] gives these figures and also shows broadly how much has been given to help research in certain branches of scientific endeavour. Thus, science and technology have received £1¾m., medicine £1½m., care of old people and research into ageing £1m., and social research and education £1¼m. The Foundation owns to having a special interest in studies of human behaviour and relationships, and one of the more notable pieces of research receiving its financial help is the subject of an article by Dr. W. K. Taylor at p. 967 of the *Journal* this week. He describes how the mechanism of learning is being investigated at University College, London, by means of electronic machines. A small one is in operation and a much more elaborate one is soon to follow. They are designed to throw light on the neurophysiological theories of learning, and in particular to test the hypothesis that learning increases the strength of transmission of the nervous impulses along the pathways they follow.

Among many other studies that the Foundation is helping is research into the brain mechanisms of insects, for it is a matter of common observation that their behaviour is sometimes strikingly similar to man's. The location of objects by electric fish is being investigated with the Foundation's help, and also animal responses to different geometrical shapes. Medicine as usual has a large share of the Fund's generosity, which is bestowed on such diverse projects as heart–lung machines and artificial kidneys, a clinic for teaching general practice to final-year medical students at the old Peckham Health Centre, and investigations into the treatment of strokes, section of the pituitary stalk, and immunological problems of disseminated sclerosis. To cover the grants for these and the many other pieces of research which it has under its wing the Fund allocated £850,000 in the twelve months covered by the report.

[1] *Report for the Year Ended March 31, 1958.* Nuffield Foundation, Oxford. 1958.

PICKWICKIAN SYNDROME

Among the many afflictions which beset the obese is an uncontrollable, though fortunately uncommon, tendency to somnolence. Isolated examples of this syndrome can be found in the early medical literature,[1 2] but it has been immortalized in Charles Dickens's description[3] of Mr. Wardle's boy, Joe, and hence the eponymous title bestowed by C. S. Burwell and colleagues.[4] If not quite accurate historically, it has at least the virtue of being memorable. The features of the syndrome are remarkably constant. The patient is usually short in stature and excessively overweight, weighing in many cases more than 20 stones (127 kg.); cyanosis and polycythaemia are common. Episodes of somnolence occur with extreme suddenness and are accompanied by irregular twitchings and a characteristic rapid and shallow periodic respiration, which differs from true Cheyne–Stokes breathing. Thus the patient may fall asleep in the middle of a conversation or even while holding a "full house" of aces and kings in an exciting poker game.[4] He is readily roused, however, and if left alone will recover consciousness spontaneously. A notable clinical finding is that in spite of dyspnoea and cyanosis the lung fields are clear, though in severe cases there may be right ventricular hypertrophy and even cardiac failure. The latter has been called "obesity heart disease"[5] and is one variety of cor pulmonale.

Studies of pulmonary function[4–8] have confirmed that there is no structural disease either in the bronchi or in the alveoli, though bronchitis sometimes occurs as a complication. Both mixing and diffusion of gases take place normally, and the fault appears to be simply a marked hypoventilation of the alveoli. This leads to a fall in arterial oxygen saturation and a rise in carbon dioxide tension (pCO_2), with resultant polycythaemia and cyanosis. The extreme obesity appears to be responsible not only for the alveolar hypoventilation but also for the inability to perform the increased work necessary to compensate for carbon dioxide retention. The episodes of somnolence are presumably due to carbon dioxide narcosis, but it is not clear why they occur in only some obese patients and what is the immediate precipitating factor. Adequate respiratory exchange can be achieved for short periods by forced breathing, and the use of intermittent positive-pressure respiration through a tracheotomy tube appeared to save the life of one patient who could not be roused and whose pCO_2 rose to 100 mm. Hg. More important is the fact that if even a little weight can be lost the attacks of somnolence cease, and, since in the early stages at least lungs and heart are normal, the value of this simple therapeutic measure is worth impressing on the patient.

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[2] Elliot, J., *A Complete Collection of the Medical and Philosophical Works of John Fothergill*, 1781. J. Walker, London.
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[4] Burwell, C. S., Robin, E. D., Whaley, R. D., and Bickelmann, A. G., *Amer. J. Med.*, 1956, **21**, 811.
[5] Sieker, H. O., Estes, E. H., Jr., Kelser, G. A., and McIntosh, H. D., *J. clin. Invest.*, 1955, **34**, 916.
[6] Auchincloss, J. H., Jr., Cook, E., and Renzetti, A. D., ibid., 1955, **34**, 1537.
[7] Carroll, D., *Amer. J. Med.*, 1956, **21**, 819.
[8] Gotzsche, H., and Petersen, V. P., *Acta med. scand.*, 1958, **161**, 383.

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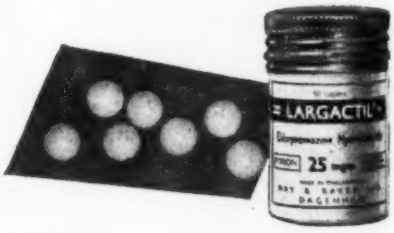

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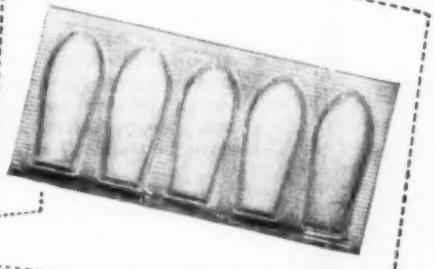

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Drug Treatment of Disease

PHARMACOLOGY OF TRANQUILLIZING DRUGS

BY

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By definition "tranquillizers" cause sedation without, as a rule, clouding consciousness. Because these substances change the responsiveness to external stimuli and influence processes of emotion and thought, specialized neurological and psychological methods are required to assess their efficacy. In order to use the drugs judiciously, it is desirable to know as much as possible about the nature of their action.

The tranquillizers can be classified into two main groups. The first comprises the drugs used mainly in psychoses (reserpine, chlorpromazine, and their congeners), while the second group consists of substances predominantly administered to patients suffering from neuroses or to normal people undergoing a severe emotional or physical ordeal.

I. DRUGS USED MAINLY IN PSYCHOSES

The members of the first group have in common the production of profound alterations in brain metabolism, but, in spite of great similarity in the indication for their use, in the therapeutic effects obtained, and in some of the side-effects encountered, the biochemical actions appear to be totally different.

Reserpine

The reserpine-like substances interfere with the retention in brain tissue of a number of amines, such as 5-hydroxytryptamine (5-HT) and the "catecholamines" (adrenaline, noradrenaline and hydroxytyramine), of which noradrenaline is the main representative in nervous tissue (Pletscher *et al.*, 1956; Paasonen and Vogt, 1956; Holzbauer and Vogt, 1956). These substances are mainly concentrated in the hypothalamus and the tegmentum of the midbrain (Amin *et al.*, 1954; Vogt, 1954), and 5-HT also in parts of the limbic system (Paasonen *et al.*, 1957); they presumably play a role in the specialized function of these regions.

The biochemical action of reserpine is not restricted to the brain: 5-HT also disappears from platelets and intestine, noradrenaline from peripheral sympathetic neurones (Muscholl and Vogt, 1958), and sometimes from the adrenal medulla. We do not know whether the depleting action in brain is restricted to the amines just listed: there may be others of even greater functional importance which are as yet unidentified and which are also lost.

Though we cannot interpret the action of reserpine in terms of its interference with the binding of amines in brain because we do not understand the role played by these compounds in central function, the fact remains that reserpine has metabolic effects on hypothalamus, mesencephalon, and limbic system. In view of the role attributed to the limbic system in emotional processes (MacLean *et al.*, 1956), this finding may be significant. It is corroborated by electroencephalographic evidence of seizure-like waves in the limbic system of reserpinized animals (Gangloff and Monnier, 1955; Killam and Killam, 1957). MacLean *et al.* (1956) caused functional inactivation of the hippocampus (part of the limbic system) of cats by injecting solid carbaminoylcholine into the tissue and setting off permanent synchronized neuronal activity simulating an epileptiform seizure; they observed that such cats had behavioural changes and alterations of conditioned reflexes which greatly resembled those after reserpine; they also showed that reserpine slows down the turnover of sulphur in the hippocampus.

We do not know whether the interference with hippocampal function is related to the disappearance from those sites of the accumulated 5-HT. Altogether, the assessment of the relation between disturbance of function and state of the amines stored in special parts of the brain is at present entirely speculative. We do, however, know that in the peripheral nervous system, where conditions are less complex, the disappearance of noradrenaline from adrenergic neurones leads to failure of peripheral sympathetic activity. It is to be expected that, in prolonged treatment of psychiatric patients with large doses of reserpine, depletion must be such as to cause varying degrees of peripheral "functional sympathectomy." Analyses of urinary excretion of noradrenaline after administration of reserpine have confirmed this expectation by demonstrating a fall in the excretion of noradrenaline (Gaddum *et al.*, 1958). How far the disappearance of noradrenaline from the hypothalamus interferes with the activity of the sympathetic centres cannot at present be decided.

Chlorpromazine

Chlorpromazine is known to be a potent inhibitor of many enzymatic processes, and its depressing action on the brain is likely to be related to this property. The turnover of phospholipids, so important in cerebral function, is among the processes affected; and the respiration of electrically stimulated slices of guinea-pig brain is inhibited by very low concentrations of chlorpromazine (Ansell and Dohmen, 1956; McIlwain and Greengard, 1957). In view of the general action of chlorpromazine on enzymes it is not surprising to find that its pharmacological actions are unusually numerous (Courvoisier *et al.*, 1953). Many of these are undesirable side-effects from the point of view of the clinician; such are the depression of the bone marrow, the autonomic actions, the galactorrhoea, and the production of Parkinsonism, an effect chlorpromazine shares with reserpine.

The electroencephalographic findings after chlorpromazine are different from those after reserpine. The site most consistently affected appears to be the region of the reticular formation responsible for wakefulness and arousal: the threshold to stimuli such as pain, electric currents, and injections of adrenaline is raised, and the responses are shortened or even abolished (Hiebel *et al.*, 1954; Himwich, 1955; Bradley, 1957; Bovet *et al.*, 1957). However, the magnitude of this effect varies with the experimental conditions, and the importance attributed to it therefore with the individual experimenter. Some consider the therapeutic effects to be more closely linked with electroencephalographic changes in the limbic system, where high doses cause bursts of spikes which originate in the amygdala and can lead to generalized seizures (Preston, 1956). The attractiveness of this view lies in the fact that it provides a common basis for the action of reserpine and of chlorpromazine.

A third site of action of chlorpromazine is shown by the ingenious technique of "self-stimulation" (Olds *et al.*, 1957). Olds discovered that animals carrying electrodes implanted in certain parts of their brain appear to derive satisfaction from electrical stimulation of these parts. When

the animals have found out that treading on a lever will deliver a shock, they begin to operate the lever at frequent intervals. Rats given chlorpromazine no longer administer the shocks to their brain when the stimulating electrodes are implanted in the posterior hypothalamus, but continue self-stimulation when the electrodes lie in the anterior hypothalamus. The drug must therefore produce some important change in the posterior hypothalamus.

Changes in Personality

The use of these pharmacological observations for the explanation of the therapeutic action is limited by our lack of knowledge of cerebral function. If one assumes the therapeutic effect in psychoses to be due to an inhibition of overwhelming drives and irrepressible stimuli which are kept up by pathological processes in the brain, one can visualize these drugs as acting by inhibition of the metabolism in the offending regions of the brain. It is impossible to tell whether the limbic system is one of these offending regions and the spikes observed correspond to certain inhibitory phenomena occurring there, or whether the limbic system is stimulated by the drugs and such stimulation leads to useful inhibitions of other parts of the brain.

There is no doubt that chlorpromazine and reserpine produce profound changes in personality. Some assessment of the changes can be made by psychological experiments on normal people and animals. For obvious reasons, tests on man can only be carried out in a very limited way; in such an investigation on the effect of a single dose of the chlorpromazine analogue mepazine ("pacatal"; N(1-methylpiperid-3-yl)phenothiazine HCl), highly skilled work had to be performed by the subject on the so-called triple tester. The result (Steinberg, 1957) was impaired performance, reduction in the tachycardia which normally accompanies effort, and lowering of the "level of aspiration," which means the improvement the subject expects to make on a repetition of the test.

More striking still are the effects observed in animals, to which the drugs can be given more freely: previously aggressive animals become tame and easy to handle; they develop an indifference to unpleasant stimuli shown in the loss of conditioned avoidance responses. Rats and monkeys, for example, were trained to avoid an electric shock by leaving a particular area of their cage when an acoustic or visual signal heralded the coming of the shock. After an injection of chlorpromazine or reserpine they failed to heed the conditioning signal, though they were perfectly capable of performing the motor effort required to avoid the shock (Smith *et al.*, 1957). Their behaviour had become inappropriate, and normal contact between animal and environment had been lost.

The results of these psychological tests suggest that a patient, though benefited while under treatment with one of these potent drugs, cannot be considered equivalent to a perfectly normal human being. The same conclusion is reached if we remember the general inhibitory effects produced on cerebral metabolism by these substances: it is inconceivable that inhibition should be entirely restricted to the unwanted cerebral activities.

II. DRUGS USED MAINLY IN NEUROTIC AND NORMAL PEOPLE

The drugs of this group lack the profound effects on brain metabolism seen in the first group; in fact, nothing is known about the biochemical side of their mode of action. Four substances, completely unrelated in chemical structure and in their pattern of pharmacological actions, will be discussed.

Methylpentynol

The first, methylpentynol ("oblivon"), is a higher alcohol and entered therapeutics as a hypnotic. Trotter (1953) introduced it into dentistry to reduce apprehension, and its success was proved by controlled double-blind trials. It then became important to ascertain by psychological tests whether it was safe to allow such patients to go home unescorted or to drive a car. It was found that the subjects, though unmistakably less inhibited in their behaviour by a dose of 0·5 g., performed well in tests which mimicked driving activities (Trotter, 1954). On the highly exacting triple tester, however, the performance, level of aspiration, and tachycardia of effort were reduced (Dicker and Steinberg, 1957).

Benactyzine

Benactyzine ("suavitil," benzilic acid diethylamine ethyl ester HCl) is a substance with an atropine-like action. Its effect on behaviour was discovered on animals (Jacobsen and Skaarup, 1955): a cat, used to obtaining food by pressing a lever and given benactyzine, went on pressing for food in spite of being greeted by a blast of air when operating the lever; when untreated, the cat refused to touch, and even hissed at, the lever. The drug also inhibits conditioned avoidance responses and thus has in common with reserpine and chlorpromazine the production of indifference towards disturbing stimuli. The results of tests on anxious people have been contradictory, and proof of efficiency in a controlled trial is still lacking (Davies, 1956; Coady and Jewesbury, 1956; Alexander, 1957; Raymond *et al.*, 1957).

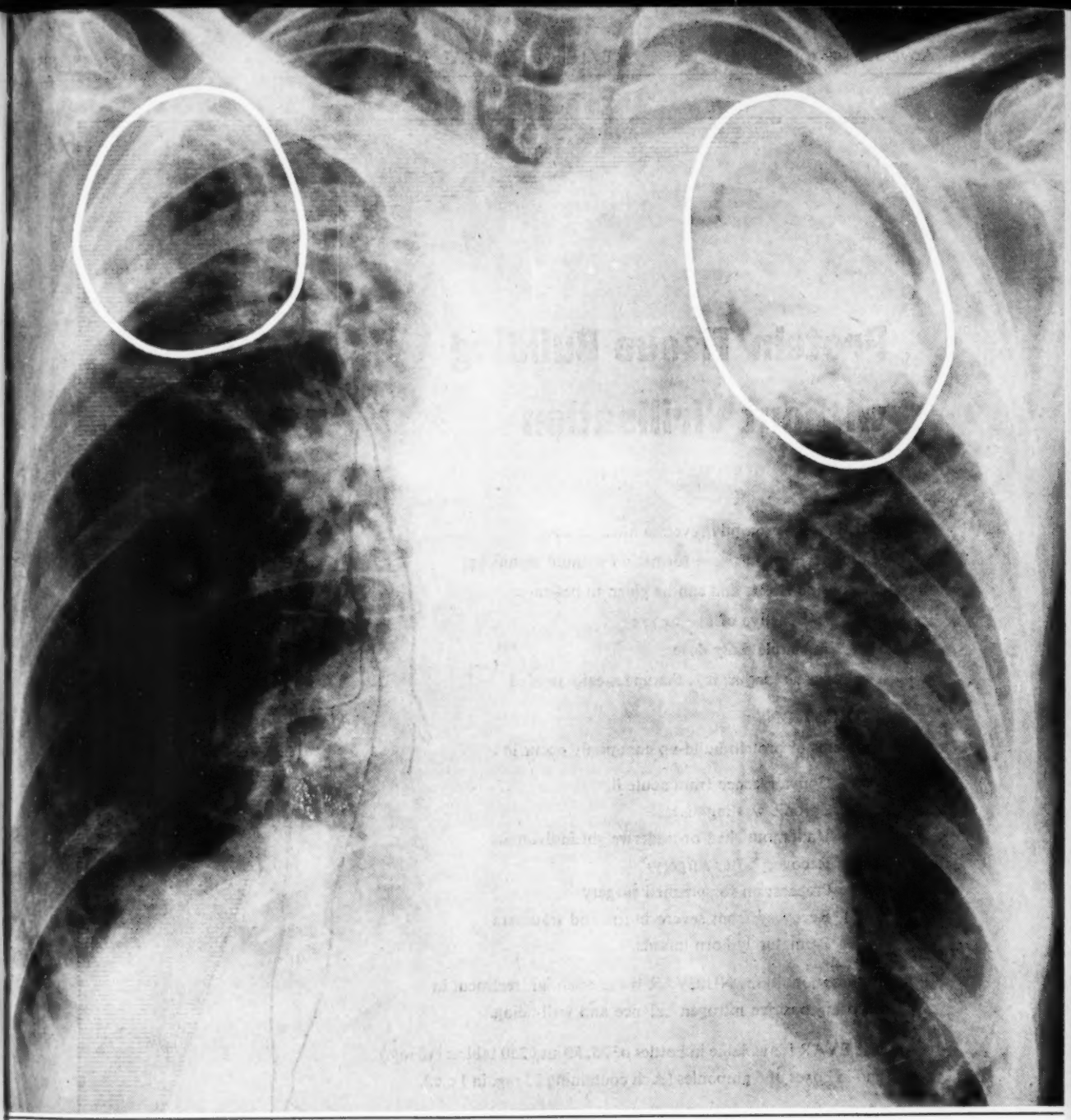
Hydroxyzine

Recently, promising reports have been published about the tranquillizing effects of a new antihistamine drug hydroxyzine ("atarax"). In a clinical trial on students suffering from psychological disorders (Becattini and Gallini, 1957), the drug, given in a daily dose of about 0.1 g., scored higher than benactyzine. Hydroxyzine is a chlorobenzhydrol derivative, and chemically related to the antihallucinatory drug azacyclonol ("frenquel"). It appears to relieve anxiety without impairing critical faculties; it is also useful in conditions of agitated coma; such patients may require up to 1 g. per day in divided doses (Ayd, 1957). It has fewer side-effects than benactyzine, but increases any tendency to seizures. It has in common with the tranquillizers hitherto discussed an inhibitory effect on conditioned avoidance reflexes (Levis *et al.*, 1957). It raises the arousal threshold to sensory stimuli (Bradley, 1957), probably by an action on the reticular formation.

Meprobamate

The fourth drug, meprobamate ("equanil," "miltown"), is chemically and pharmacologically related to the central relaxant of skeletal muscle, mephenesin. Its tranquillizing action, however, is exerted by doses (0.4–0.8 g. several times a day) which are too small to affect muscular tone. Its mode of action differs from that of all other tranquillizers. Monkeys and rats become manageable and fearless, but the loss of fear does not lead to loss of conditioned avoidance reflexes. Thus—and this is in contrast to the behavioural effects of reserpine—chlorpromazine, benactyzine, and hydroxyzine, appropriate avoidance of noxious stimuli is not impaired (Berger, 1957), though inhibition ("freezing" of rats, for instance) by imminent danger is greatly reduced (Hunt, 1957). Specific effects on emotional behaviour were also shown in ducklings, which lost their fear of strange objects and the capacity of "imprinting"—that is, becoming attached to a parent duck or a decoy (Hess, 1957).

In man, double-blind clinical trials on meprobamate (Hollister *et al.*, 1957) have shown improvement of anxiety neuroses and even of certain psychoses. In contrast to the effects of the other tranquillizers, it did not impair performance or level of aspiration in psychological experiments on the triple tester (Steinberg, 1957). These observations, and the findings with conditioned reflexes, show that the drug is capable of checking emotional responses while not interfering with skill, rational behaviour, and adequate responses to environmental stimuli. These would seem to be advantages for the ambulatory patient. It would be of the



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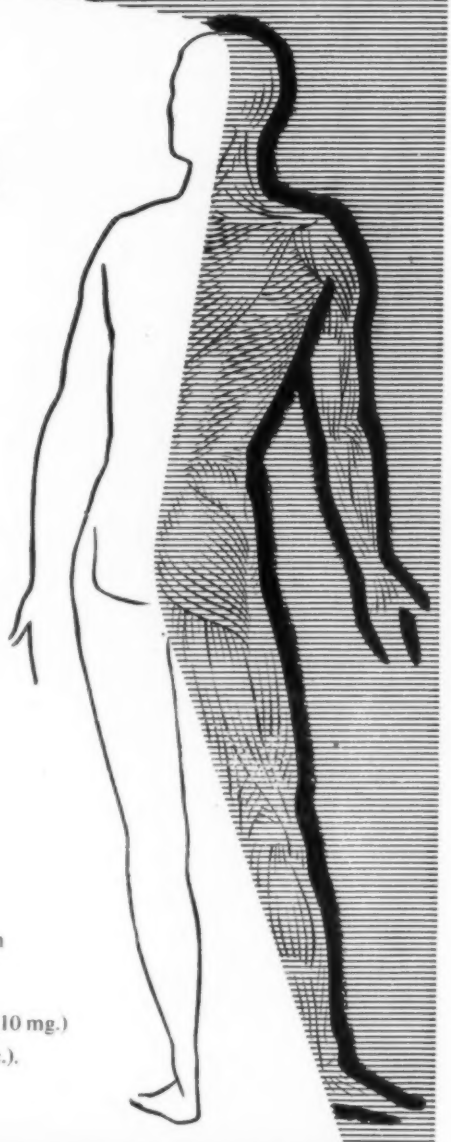

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greatest interest to know the precise site and mode of action of meprobamate. When low doses are administered to monkeys, electroencephalographic changes (of a type associated with decreased activity) are found only in a number of thalamic nuclei (Hendley *et al.*, 1957). This is no proof that the thalamus is the only or even the fundamental structure through which meprobamate exerts its clinical action, but it shows that the pattern of activity of this drug is different from, and less diffuse than, that of other tranquillizers, and that the thalamus plays some important part in its effects.

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ANALOGUE COMPUTERS FOR RESEARCH ON LEARNING

BY

W. K. TAYLOR, Ph.D., A.M.I.E.E.

The theories of learning that are being investigated at University College, London, with the aid of electronic analogue computing machines are based on a simple hypothesis that is now widely accepted by neurophysiologists—namely, that learning is due to changes in interneuronal transmission characteristics. According to this hypothesis, nerve impulses generated by the neurones that play a part in learning increase the transmission strengths of the paths that they follow. In discussing this hypothesis many problems arise concerning the physiological nature of the changes and the effects they would be expected to produce in various types of networks. The construction of neural analogues can help greatly in formulating and solving these problems.

Network with History

The transmission strength of the path from any neurone A to any other neurone B may be defined as the change in the firing rate of B produced by a change of one impulse per second in the firing rate of A. This definition assumes that neurone B is firing when the change in A's rate occurs, for if B is inhibited to zero frequency the impulses from A may not be sufficient to overcome the inhibition. The transmission strength of the path from A to B is said to be positive if A tends to increase the firing rate of B and negative if A inhibits B.

The foregoing characteristics are simulated in the computer by arranging a network whose output depends upon its past history. The connexions between input and output are such that various pathways may be taken following a given input. Electronic counters count the number of impulses flowing in each path of the network under investigation. These counters control the transmission characteristics in proportion to their content. When visual learning is being studied a set of light-sensitive elements or "eye" is arranged to receive the input shapes and to generate input impulses at frequencies proportional to the distribution of light intensity. All the impulses are the same size, but the strength of the driving effect produced by each impulse on a recipient neurone analogue unit is increased in proportion to the content of the impulse counter.

Thus, if only a few impulses have traversed a given path since the start of a learning experiment, the counter content will be low and the impulses will have only a small driving effect on the units to which they are connected. Preferential paths of high transmission strength can be built up in a network of this type. A given stimulus pattern can be made to select a particular output if the flow of impulses is directed by a training procedure. This is what we believe happens when an animal, say an octopus, is trained to attack certain shapes and to avoid others. The impulses generated by the act of feeding or by an electric shock are thought to direct the visual impulses through paths that lead to the attack and escape mechanisms respectively. One of the reasons for constructing computing machines is to test such vague hypotheses and to examine in detail the properties of networks that reproduce the learning behaviour of animals when supplied with appropriate stimulus patterns. Without an actual model one is reduced to making so many unrealistic assumptions in order to make the problems manageable that any results are of purely theoretical interest.

Neuronal Connexions

In order to decide on the characteristics to be given to the analogues it is necessary to make some assumptions about the physical nature of the connexions between neurones. In the mammalian spinal cord the transmission probably takes place through chemically controlled synapses in which the sign of the transmission is either positive or negative and the strength can take any value from zero up to a maximum. It is possible that the maximum transmission strength may have a very large value if the axon of the afferent neurone branches into thousands of endings which synapse with the recipient neurone and cover its surface with boutons. Aided by a sufficiently strong and durable synaptic chemical transmitter a single afferent impulse might then produce a high-frequency discharge in the region of 1,000 impulses per second lasting for many milliseconds. It is known that a high-frequency discharge of Renshaw cells in the spinal cord in response to a synchronous volley can last for fifty milliseconds or more before the chemical transmitter is neutralized. Under these conditions a transmission strength of up to 100 may occur, and this is the maximum value allowed for in constructing the electronic analogue machines.

As has been stated, the learning theories under investigation are based on changes in transmission strength, and this implies that the changes must last as long as the learning

is in evidence. With an intact brain an octopus is able quickly to learn to attack some shapes and avoid others. The memory then lasts for many days.[1] If the region of the brain known as the vertical lobes is removed, the memory is only strongly in evidence for several minutes.[2] However, by persistent training with trials at short intervals it is possible to set up more permanent memories in these deficient animals elsewhere in the nervous system.[3,4] There is much evidence that memory systems include distinct transitory and long-lasting components. The human memory for selected events can last for many years, and for practical purposes the underlying neural changes responsible for them can be regarded as permanent. In constructing a general purpose computing machine we must therefore make provision for changes in transmission strength that can last for seconds or minutes and for changes that are effectively permanent. The small analogue computing machine that has already been in use at University College has a memory that stores changes in transmission strength for up to half an hour, the change gradually decaying exponentially to zero.

Before considering the application of the small machine to the problem of learning in a network of neurones it will be helpful to consider the static types of networks found in the spinal cord and retina. These networks are specified genetically and the transmission strengths of their connexions must remain approximately constant if they are to function correctly and consistently throughout life. Any machine that is to represent complex learning networks should also be capable of representing what is already known about the connectivity in these fixed networks. The existing machine has been used to make analogues of the spinal cord networks involved in supraspinal control of limb position and the networks of interacting neurones found in the retina. In both these examples observations of the machine behaviour have led to the formulation of relatively simple theories of how such things as the supraspinal control of limb positions in space,[5] and the visual phenomena of contour formation and streaming,[6] could be related to nervous activity.

Changes with Learning

Very little is known about the changes in form of the connexions in the brain with learning. There are no apparent differences between the brains of trained or untrained animals, but there is no reason to doubt that changes in organization occur on a microscopic scale or possibly at a chemical level in the regions where axons and dendrites come within the radius of the effective chemical transmitter. The computing machine has answered the question whether a system of this type can show learning behaviour. It showed that the above conditions are sufficient for the learning of simple visual shapes if the neurones are distributed in certain characteristic ways.[7] However, the small size of the machine allows only limited quantitative predictions about the learning capacity that can be expected from a large number of neurones. The "training" of the networks that are being simulated on the computing machine is achieved by presenting shapes to an "eye" which consists of nine photosensitive elements. Only a few simple shapes can be classified, and the memory for these continually fades if not reinforced by repeated presentations. The complexity of the shapes that can be detected by the input system increases enormously as the number of "eye" elements increases. It is believed that all the letters of the alphabet and short words could be resolved by eighty to one hundred input elements. A larger machine is being designed to test this and give further quantitative predictions on learning phenomena with still larger numbers of units. With up to 4,000 neuronal analogue units available, the new machine should, for example, enable us to estimate the brain storage capacity required to learn the alphabet and more complex shapes. Since the machine is a direct analogue it will work in real time, so that variations in rates of learning produced by changes in the material to be learnt and the methods of presentation can be measured and the results compared with the behaviour of human subjects in similar experiments.

One thing about which we know very little at present is the relative magnitude and time course of the changes that occur when an object to be memorized is presented visually. It may be that most of the changes occur in the first milliseconds and that further observation on the same occasion produces negligible additional changes of transmission strength. If the changes are very small they should be disturbed by random events or "noise," which can be introduced into the computer in controlled amounts. At the other extreme large changes would be difficult to cancel if the classification proved to be wrong or disadvantageous, and the memory would reach saturation level in a short time. All the foregoing variables will be adjustable in the computer and their influence on learning rates, accuracy, and memory capacity should be measurable.

Theories of brain function in different animals will be tested by constructing networks of neurone analogue units. With the small machine it has only been possible to study theories of the spinal cord, retina, and visual areas of the brain, but it is estimated that the new machine will contain sufficient units for the study of theories of interaction between different regions of the brain and in particular the learning process whereby speech and other motor activity becomes associated with visual experience.

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INTERNATIONAL ASSOCIATION OF GERONTOLOGY

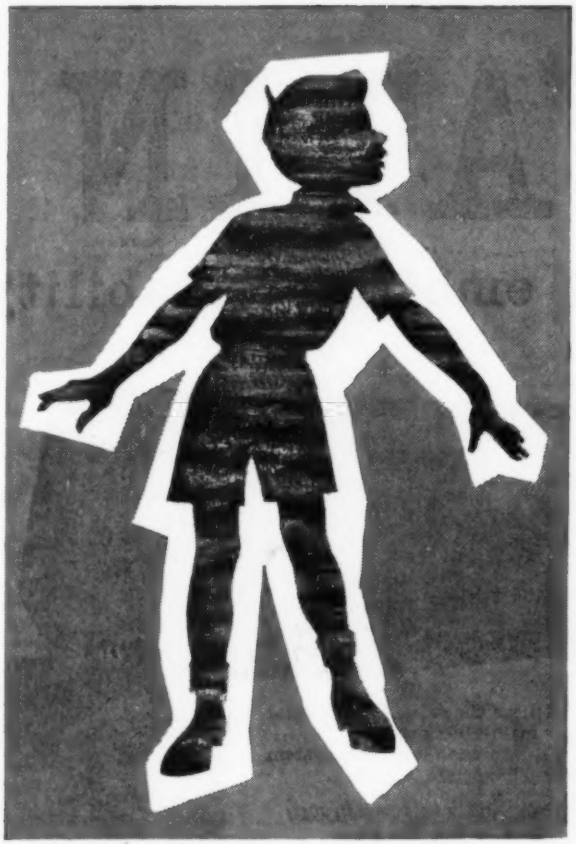
EUROPEAN CLINICAL SECTION

[From a Special Correspondent]

The first meeting of the recently constituted European Clinical Section of the International Association of Gerontology was held from October 2 to 4 at the General Hospital in Sunderland, where the late Dr. O. Olbrich—who was to have been the Section's first secretary—had founded the Sunderland Geriatric Unit. Warm tributes to Dr. Olbrich's memory and to his research work were paid by many British and foreign contributors.

Genito-urinary Disturbances

The opening session, on genito-urinary disturbances in old age, was introduced by Dr. Torben Geill (Copenhagen), who recalled that renal plasma flow starts to fall at the age of 30–40 and has dropped to half by 80 years. Urinary infections were very common in the elderly, being present in 20–40% of old people investigated in Danish hospitals: pyelonephritis was found in 5% of necropsies, but was relatively seldom diagnosed during life. He reviewed the treatment of uraemic states and the oedema of nephritic origin in the elderly: the anaemia here was often refractory to iron alone, but he had found the addition of cobalt, 5 mg. per day, often caused a response. For cases of urinary incontinence due to lack of neurogenic control from cerebral disease he used a training regime of activity, fixed times for bladder evacuation, and fluid restriction after 5 p.m. He had found intramuscular testosterone propionate, 50 mg. in oil twice weekly, effective in controlling incontinence in women if it was not complicated by infection or dementia. Dr. C. P. Stewart (Edinburgh) reviewed his earlier researches with Olbrich on kidney function in the elderly, where it was especially difficult to dissociate the effects of ageing from those of



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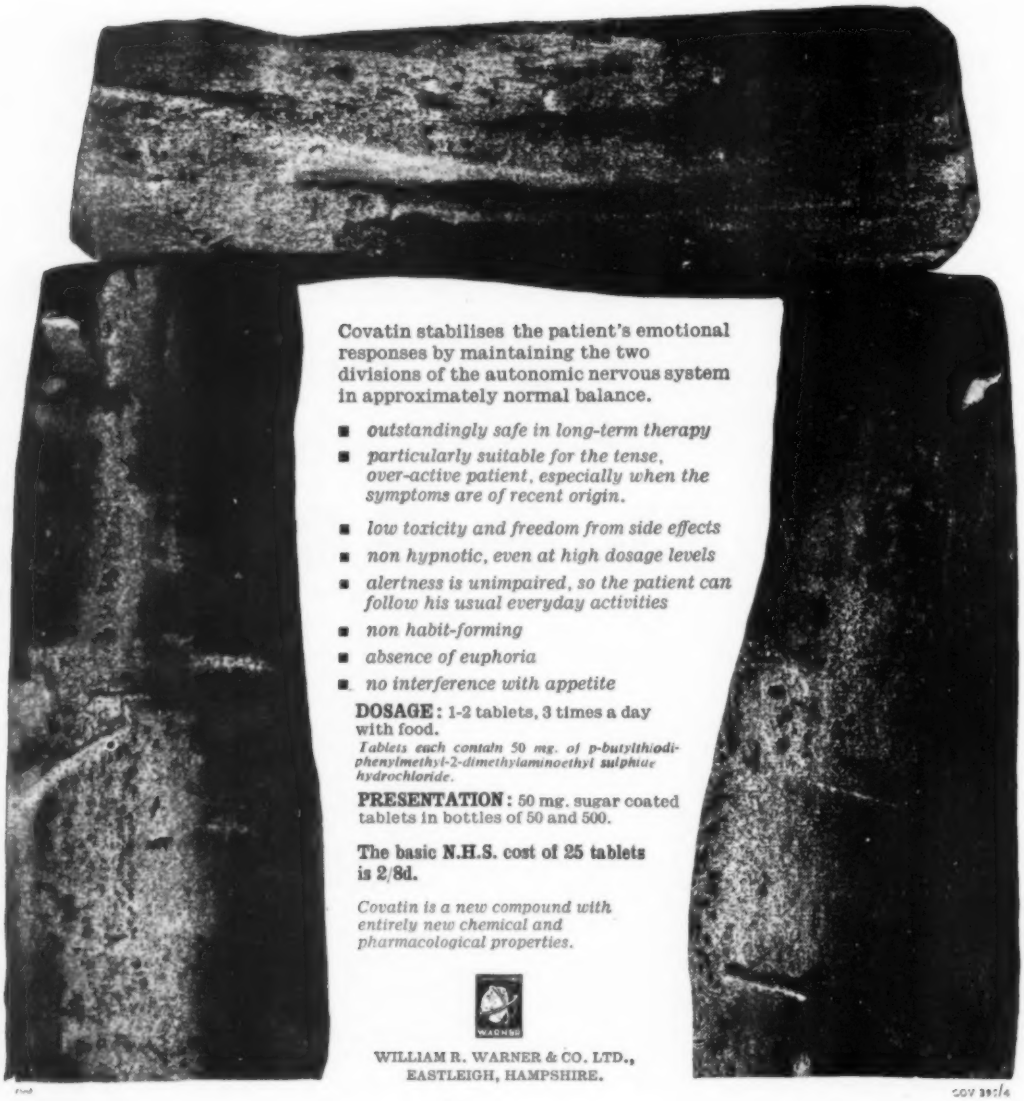

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disease. There was a fall in glomerular filtration rate with age, but he believed this was due to a fall in blood supply to the kidney and not a primary renal dysfunction. There was some loss of tubular function in old people with a high diastolic pressure, and this was probably due to a reduction in the number of the functioning nephrons.

Mr. J. H. Ross (Sunderland) discussed prostatectomy in the very elderly. Many old men preferred to suffer rather than take the risk of operation; but this was unnecessarily pessimistic. He had operated on 103 patients over 80 with only 11 deaths in the first two post-operative months. He did not believe in immediate prostatectomy for acute retention. Special care was needed in the choice of anaesthetic, and hypotensive drugs were contraindicated. Pre-operative preparation and scrupulous post-operative care carried out by specially trained nursing staff, who must spend a great deal of time in retraining and reassurance, were essential for such elderly men; then they would regain continence.

Dr. O. Taylor Brown (Dundee) described apparatus for cystometry combined with tidal bladder drainage. At a certain critical volume, usually four ounces (114 ml.) in incontinent patients, the bladder responded with a large increase in pressure and spontaneous emptying. When infection was eliminated the response was less violent. In very resistant cases of infection daily lavage, to change the flora prior to the further use of antibiotics, was necessary. He advocated perineal urethrostomy with a self-retaining catheter as preferable to suprapubic catheterization where prostatectomy was impracticable. It seemed that certain old people had a reversal of rhythm and secreted the larger volume of urine by night; therefore he questioned the technique of fluid restriction after 5 p.m. Dr. L. E. Totterman (Helsinki) had found incontinence in 25% of long-stay patients; it was five times as common in women as in men, especially if mentally disturbed and unable to move. He recalled how ineffective treatment for chronic urinary infections was, and he had found antispasmodic drugs of no real value for incontinence. He gave his first experiences of the symptomatic use of the Raiche double-balloon female incontinence drain.

Arteriosclerosis

In the session devoted to ageing and arteriosclerosis, Dr. H. M. Sinclair (Oxford) considered that, in spite of the lack of proof of an association between nutrition and coronary heart disease, there must be such an association to explain the very great increase in deaths from this and other vascular disorders in the last 100 years. He thought that stress, the other likely factor, could be sufficiently ruled out. In some countries at certain times there had been much alteration in the intake of fats, and this was mirrored in the death rates from coronary thrombosis and ischaemic heart disease. Changes in blood coagulability dependent upon dietary factors, which could be shown in rats, might be the clue. Certain lesions, such as arcus senilis, could be produced in animals when dietary unsaturated fats were kept low and saturated fats high; the process was reversible. Dr. H. Fleischhacker (Vienna) claimed to have had improvement in cases of severe cerebral vascular accidents from the early use of intravenous prednisone, but found no support for this view from other speakers. Professor B. Prusík (Prague), reviewing myocardial infarction in elderly subjects, had found the degree of the subsequent leucocytosis a guide to prognosis, but his series was small. Dr. H. Merskey and others (Sunderland) had studied serum lipids and lipoproteins by paper chromatography: pre-β-lipoprotein scores were high after coronary thrombosis but not after cerebral thrombosis, so they concluded that the pathology of these two conditions was not the same.

Confusional States

A session on confusional states in the elderly, in which all the contributors were from Great Britain, was opened by Professor Alexander Kennedy (Edinburgh). He compared the poor prognosis for the elderly patient admitted with acute confusion 10 years ago, when 12% died in two weeks and 70% were sent on to mental hospitals, with the outlook now when 80% returned home in two weeks. This was the common experience of a psychiatric and a geriatric department. The improvement was entirely due to adequate assessment and biochemical investigation, which led to appropriate treatment. Fewer acute psychiatric emergencies were now seen in their own homes, because beds in those departments were being properly used and cases could be admitted early and rehabilitated. Care under the mental health Acts was not needed in confusional states in the elderly, but a separate delirium ward was needed in every geriatric hospital. The rapidity with which sensory deprivation produced disorientation even in the young and healthy must be stressed. Professor Kennedy then proceeded to analyse the content of thought and behaviour in delirious states and the varied mental attitudes of disturbed old people, who often were unaware of the progression of their shortcomings. He stressed the need for doctors and nurses attending the recovering delirious patient to reintroduce themselves and the environment repeatedly in simple words; they must provide a stable environment—the same bed in the same place in the ward throughout, with familiar objects about, a night-light but no stark shadows, and repeated assurance available from familiar attendants. Otherwise, after appropriate treatment for underlying physical disorders, oxygen, steroids, and vitamin B_1 might be helpful.

Since drugs, hormones, and other biological means of treatment were so ineffective in persistent dementia in old age, Dr. Felix Post (London) was trying techniques of social psychiatry including occupational therapy, but had found therapy could not be withdrawn without immediate relapse. Cases must be taken early, but he had found so few cases were detected early. It had begun to appear that the onset of senile dementia was more sudden than we had thought; perhaps abilities had to fall below a threshold required for familiar tasks before dementia was recognizable. If so, the chances of treating patients in the earliest stages were slender. Dr. H. Droller (Leeds) had estimated vitamin-B_{12} levels in serum in cases of senile dementia and confusional states. Confused patients had levels only slightly lower than normal, but demented patients usually had levels as low as those in cases of pernicious anaemia, yet they had neither the signs of pernicious anaemia nor subacute combined degeneration, and their mental state seldom showed response to specific therapy. He had not found a lowered serum B_{12} to be a function of the patient's age or nutritional state.

Dr. F. J. Fish (Edinburgh) had reviewed patients with senile paranoid states and found them to be of many types, with recognizable schizophrenia and other psychoses. He therefore doubted that "senile paraphrenia," as described by Roth, was an entity. Professor M. Roth (Newcastle), however, argued that senile paraphrenics were recognizable as they did not deteriorate intellectually, and many were deaf or blind. Dr. F. J. Flint (Sheffield), in a survey from general geriatric wards, analysed the many physical diseases underlying confusional states in the elderly, which were present in 42% of all his patients on admission.

Dental and Other Disabilities

Miscellaneous papers included one from Professor F. Verzar (Basle) suggesting that the loss of muscle efficiency and muscle mass in old people might be due to a dystrophic process, as it is in old rats, which show creatinuria, and in hamsters, where the same picture can be induced by diets deficient in vitamin E. Ageing human muscles had a low content of vitamin E, and creatinuria was found in some aged humans. Dr. W. H. Lloyd (Oldham) described the voice changes in myxoedema, the low pitch, slowness, slurring, and "clotting" of the voice, which had sometimes led him to the diagnosis before other signs were obvious. His serial tape recordings of the voices before and after treat-

ment arrestingly demonstrated this useful sign, and the great value to be placed on a tape recorder as a clinical aid.

Mr. J. R. MOORE (Sunderland) described the aims of a pilot dental scheme for the elderly in hospital in Sunderland. 186 out of 500 seemingly edentulous mouths had had dental abnormalities revealed by radiographs. Sepsis must be cleared unless there was a real contraindication. A very few sound teeth might prove adequate for the elderly patient, especially if they were in occlusion. A prosthesis might be of real functional and of even greater aesthetic value, but must be planned with due regard to the patient's eating and other habits. Some old people prefered to chew with their naked gums.

The sessions were all presided over by Dr. J. A. HUET (Paris), chairman of the European Clinical Section, and all arrangements for the meeting were in the hands of the Section's honorary secretary, Dr. E. WOODFORD-WILLIAMS, who has succeeded Dr. Olbrich as director of the Geriatric Unit in Sunderland. The next meeting of the Section will be in 1959 at Vittel, in France.

POPE PIUS XII

ONE OF HIS LAST TALKS TO DOCTORS

One of the last occasions on which Pope Pius XII addressed a medical audience was on September 15 at the Seventh International Congress of Haematology in Rome. He advocated the spread of information on genetic problems and condemned what he defined as direct sterilization.

Eugenics and Sterilization

In a general way, he began, it was necessary to underline first the necessity of furnishing the public with the indispensable information concerning the blood and its heredity, in order to allow individuals and families to be on guard against lamentable consequences. For this purpose there could be organized centres of information and consultation which engaged and married couples could consult with full confidence on questions of heredity in order to have greater assurance of happiness and security in their union. These centres would not only give information but would help the interested persons to apply efficacious remedies.

In almost all homes difficult situations were met with concerning the heredity of one or more of their members. It could even happen that the husband and the wife accused each other of an anomaly which showed up in their child. Often the specialist consulted could intervene successfully to lessen the difficulty. Warned of the danger and its significance, parents would then make a decision which would be "eugenic" or "disgenic" with regard to the hereditary characteristic under consideration. If they decided to have no more children, their decision was "eugenic"—that is to say, they would no longer propagate the defective gene by begetting either diseased children or normal carriers. If, as usually happened, the probability of begetting a child carrier of this defect was less than they feared, it might be that they would decide to accept other children. This decision was "disgenic," since they propagated the defective gene rather than arrested its diffusion. In short, the effect of the genetic consultation was to encourage parents to have more children, which they would not have had without it, since the probabilities of having an unfortunate case were less than they thought. If the consultation should seem "disgenic" with regard to the abnormal gene, it was necessary to consider that persons sufficiently preoccupied with the future to ask for advice had a high conception of their duties as parents; from the moral point of view, it would be desirable that these cases become more frequent.

Better warned of the problems posed by genetics and of the gravity of certain hereditary diseases, men of to-day had, more than in the past, the duty to take account of this increased knowledge so that they might forestall countless physical and moral difficulties for themselves and others. They should be attentive to whatever could cause lasting harm to their descendants and involve them in an interminable succession of miseries. The community of blood between persons, whether in families or in collective groups, imposed certain duties. Although the formal elements of every human community were of the psychological and moral order, the lineal descent was its material basis, which must be respected and in no way harmed.

"What We say of heredity could be applied in a wide sense to the communities which are composed of the various races of the human family. But here there is greater danger of an exaggerated insistence on the meaning and value of the racial factor. It is only too clear, alas, to what excesses pride of race and racial hatred can lead: the Church is always energetically opposed to it, whether there is question of attempts at genocide or of practices inspired by what is called the "colour bar." She also disapproves of every experiment of genetics which would make light of the spiritual nature of man and would treat him as on a level with any member whatsoever of the animal species."

Artificial Insemination

Discussing "the problem of defective heredity," the Pope said he had already had occasion to take a stand against artificial insemination. He absolutely reprobated artificial insemination between persons who were not married, and even between husband and wife. "This practice is not within the rights of married persons and is contrary to the natural law and to Catholic morals." As regards artificial insemination between parties both of whom were unmarried, he had already in 1949 declared that it violated the principle of natural law that new life might be procreated only within a valid marriage.

The solution through voluntary adultery stood self-condemned, whatever be the reasons, biological, eugenic, or juridical, by which one might attempt to justify it. No married person could put his marital rights at the disposal of a third party, and any attempt to renounce them was ineffective.

Another proposed solution was sterilization, either of the person or only of the act. For biological and eugenic reasons these two methods were gaining in popularity and were progressively spreading through the use of new drugs which were increasingly effective and convenient to use. Substantially, direct sterilization was not justified on the ground of man's right to dispose of his own body, and hence that it could not be regarded as an acceptable solution for preventing the transmission of a diseased heredity. Direct sterilization—that is, sterilization with the intention, either as a means or as an end, of making procreation impossible—was a grave violation of the moral law and was therefore illicit. Not even public authority had the right, under pretext of any indication whatever, to permit it, and much less to prescribe it or to have it done upon innocent persons.

"By direct sterilization We intended to designate the act of one who intends, either as a means or as an end, to render procreation impossible; We do not, however, apply that term to every act which in fact makes procreation impossible. The truth is that a man has not always the intention to do what flows as a consequence from his act, even if he foresaw it. Thus, for example, the extirpation of diseased ovaries will have the necessary consequence of making procreation impossible; yet this impossibility may not be intended either as an end or as a means."

Preventing Ovulation

A question which was now being much discussed by physicians and moralists was this: Is it licit to prevent ovulation by means of pills used as remedies for excessive reactions of the uterus and of the organism, even though this medicament, by preventing ovulation, also makes conception impossible? Is a married woman who, in spite of this temporary sterility, wishes to have relations with her husband allowed to use this medicine? The answer depended on the intention of the person. If the woman took the medicine, not with a view to prevent conception, but solely on the advice of the doctor as a necessary remedy because of a disorder of the uterus or of the organism, she

was causing an *indirect* sterilization, which was allowed according to the general principle concerning acts which had a double effect. But one produced a sterilization which was *direct*, and hence illicit, when one stopped ovulation in order to preserve the uterus and the organism from the consequences of pregnancy which they could not bear. Some moralists held that it was allowed to take medicaments for this purpose, but that was wrong. We must also reject the opinion of several physicians and moralists who permitted this when a medical indication made it undesirable that a conception should occur too soon, or in other similar cases which could not be mentioned here; in all these cases the use of medicaments had for its purpose to prevent conception by preventing ovulation; hence it was direct sterilization.

In order to justify it, a moral principle was sometimes cited, which was right in itself but was wrongly interpreted: *Licet corrigere defectus naturae.* And since in practice it was sufficient for the application of this principle that there be a reasonable probability, it was claimed that this was a case of correcting a natural defect. If this principle had an absolute value, eugenics could without hesitation use drugs to prevent the transmission of defective heredity. But attention must also be paid to the manner in which the natural defect was corrected, and care must be taken that other principles of morality be not violated.

Married persons who used their conjugal rights had a positive obligation, in virtue of the natural law as applied to their state, not to exclude procreation. It was the will of the Creator that the human race should propagate itself precisely through the natural exercise of the sexual function. "But We apply to this positive law the same principle which is valid for all others: they cease to be binding in the measure in which their fulfilment entails notable disadvantages which are neither inseparable from the law itself nor inherent in its fulfilment, but arise from some other source, and which consequently the lawgiver had no intention to impose upon men when he promulgated the law."

When it was necessary to advise against natural procreation because of the danger of tainted heredity in the case of married persons who would nevertheless like to have a child, the system of adoption was suggested to them. It had also been observed that such advice usually brought good results and restored happiness, peace, and serenity to the parents. From the religious and moral point of view there was no objection to adoption.

Matrimonial Contract

Asked whether the "Rh situation" may be considered as a reason for the nullity of marriage, when it entails the death of the children from the first pregnancy, the Pope said the simple fact that the hereditary defects entailed the death of the children did not prove the absence of the will to contract the marriage. The situation was evidently tragic, but the argument rested upon a consideration which was unsound. The object of the matrimonial contract was not the child, but the placing of the natural matrimonial act, or, more precisely, the right to place that act; this right remained completely independent of the hereditary patrimony of the child begotten and likewise of its possibility of living.

Asked if it was permitted to make propaganda on the technical level in order to emphasize the dangers inherent in a marriage between persons with blood relationship, he said that without any doubt it was useful to inform the public of the serious risks which marriages of this kind entailed. Here again account would be taken of the gravity of the danger in order to judge the moral obligation.

The Pope ended by referring to the "incontestable merit" of the physicians' labours. "We most willingly encourage them. We deeply appreciate the active and serious co-operation which permits the free expression of different opinions, but is not content with merely negative criticisms. That is the only way which opens on real progress, both in the acquisition of new theoretical knowledge and in its clinical application."

SIR CHARLES HASTINGS LECTURE

DR. DONALD HUNTER AT BRISTOL

On October 7 Dr. Donald Hunter, physician to the London Hospital and director of the M.R.C. department for research in industrial medicine, delivered a Sir Charles Hastings lecture at Bristol on "New Problems in Public Health." These lectures, sponsored by the British Medical Association and inaugurated in 1927, are intended to inform the general public about questions of health; they are given from time to time—annually or less often—by prominent members of the profession.

The Lord Mayor of Bristol, Alderman F. G. W. Chamberlain, took the chair and introduced Dr. Hunter to a large medical and lay audience in the Victoria Rooms, Clifton. It was important, said Dr. Hunter, to study the patient's environment as well as the physical condition from which he suffered. A good doctor took into account social and economic factors, conditions of work and leisure, standards of housing, clothing, diet, and personal habits; he saw the injured worker as a breadwinner, the woman in childbirth as a wife and mother, the handicapped child as an educational problem and a source of special anxiety to its parents. Often the role of these social aspects of the doctor's work was too little emphasized in undergraduate medical education. Dr. Hunter then sketched briefly, through the lives of the eighteenth and nineteenth century pioneers, the story of the foundation of modern public hygiene: the recognition of the influence of poverty and ignorance on health, the struggle to deal with the urgent administrative and sanitary problems of the industrial revolution, and the improvements whereby town life was gradually made healthy.

World Health

The World Health Organization was the greatest adventure in world collaboration yet undertaken. During its ten years of life more effective methods of fighting or preventing disease had been developed, and governments had learnt to take responsibility for the health of their peoples.

Infectious disease had handicapped man throughout his history; but in limited areas of the world in which it had been possible to apply the knowledge acquired by medical science the epidemics of the past, particularly cholera, smallpox, plague, and yellow fever, were no longer feared, and malaria was coming under control. The list of other scourges controlled was long and encouraging.

The value of iodine in the treatment of goitre had been known from time immemorial; and there was now ample evidence from those countries that had used iodized salt—such as New Zealand, Switzerland, and the United States—of its value and safety. Here, then, was a disease which could be wiped out from every country in the world if society would only make the effort. The controlled fluoridation of drinking-water to prevent dental decay was to-day being carried out on a large scale. Twelve years after the first experiments more than 30 million people in the United States were using drinking-water to which fluorides had been added, while local fluoridation programmes were in operation in 15 other countries. Until the preventive effects of fluorides were discovered, public health authorities had practically no means of combating dental caries.

The greatest single destroyer of human life in the world was not war, or cancer, or coronary heart disease, but malaria. For 60 years we had known of the chain of transmission of the disease, and at the start of the present century the way was clear for a campaign to control the disease. But drainage of marshes and the use of quinine seldom eradicated the disease and malaria control was not economically possible in the rural tropics in general. In 1939 the picture changed suddenly with the discovery of the insecticidal properties of D.D.T. The proper use of insecticides made possible the eradication and not merely the

control of malaria. The size of the problem was enormous. About 45% of the total population of the world lived in malarious areas. But the disease had been conquered to such an extent that, whereas in 1948 300 million people had malaria each year and 3 million died of it, by 1957 these figures had been reduced by more than 40%. The eradication of malaria, already achieved in certain areas such as Italy, Cyprus, Mauritius, Formosa, and Venezuela, was now possible almost everywhere in the world. It was likely that it would, in a few years, be controlled in the U.S.A., and no new infections with it were expected in the U.S.S.R. after 1960.

The resistance to insecticides developed by insects which are vectors of malaria and other diseases had lately become a public health problem of importance. We had therefore entered a race to interrupt the transmission of malarial parasites, and it was imperative to win the race in malarious areas before resistance set in among the local mosquitoes. Moreover, unless transmission was maintained at a low level, there would always be a danger that the disease might become rampant again in areas where it had up to now been successfully controlled with insecticides. W.H.O. was interested in perfecting a malaria suppressive drug which could be added to table salt in malarious districts. Stable drug-salt mixtures had been prepared and tested on volunteers from the U.S. penitentiary at Atlanta, Georgia, and the results so far were very encouraging. Malaria was completely suppressed throughout the tests (41 days for chloroquine, 45 days for pyrimethamine) and for 28–43 days thereafter in all the test subjects, even though they had been exposed to three large doses of sporozoites.

Many diseases formerly feared were now virtually under control. But we were faced by new problems. More elderly people must be fed and housed and given work ; the diseases of later life, such as cancer, diabetes, and coronary heart disease, were commoner. And whereas infectious and parasitic diseases had been reduced by half, accidents, especially among the young, were leading causes of death. Socially the conditions and life of the industrial worker lay at the foundation of the well-being of an industrial people. Constant vigilance was necessary to prevent the introduction of harmful methods of working.

Mr. A. Wills proposed the vote of thanks to Dr. Hunter, and Mr. A. G. Palin, chairman of the Bristol Division of the B.M.A., added his congratulations. Afterwards the Division gave a sherry party to the guests.

NEW ACADEMIC YEAR

WESTMINSTER MEDICAL SCHOOL

Sir Christopher Hinton, F.R.S., chairman of the Central Electricity Generating Board, and a former member of the Atomic Energy Authority, chose "The Acceptance of Risk" as the subject for his inaugural address to the Westminster Medical School on October 6. He said that, in considering the impact of atomic energy on the public, he had had to give a good deal of thought to their reactions to the risks they thought they were running. He had come to the conclusion that only an insignificant minority of people as individuals, and no body of people collectively, let any measure of logic enter into their assessment of risk.

Acceptable Risks

If one set aside the hazards of war, where national emotion played an abnormal part in deciding what was acceptable and what intolerable, the hazards which most readily excited the public to-day were those connected with atomic energy. The logical ground for disquiet about nuclear power was really that, although the atomic energy plants now being built might be inherently safe, and although the most careful thought went into their design, there was as yet very little practical experience of them. Human skill had its limits and was based on knowledge which could never be all-knowing. So, if human frailty led to plant failure, there must be a possibility, however remote, that that failure would have widespread effects. Consciously or subconsciously the public knew that, and this was the basis for their alarm. Yet the plants were so placed that even if failure occurred steps could be taken to safeguard people who were likely to be affected. By no stretch of the imagination could an accident be visualized which would result in the number of casualties caused by the coal gas industry, where without great outcry or complaint we tolerated 740 deaths a year from accidental leakage of domestic gas and another 2,500 voluntary deaths from gas poisoning.

Surely the explanation was that risk in itself was not onerous and might indeed be a stimulus. It was only when risk gave rise to a protracted fear that it became a burden. The magnitude of the fear did not matter: it was its duration. What, then, were the conditions which ensured that risk would not lead to fear? Sir Christopher Hinton suggested first that the risk must be understood ; secondly that the acceptance of the risk must bring a measurable advantage to the individual ; and thirdly that each individual must, as an individual, feel that he could escape from the risk by the exercise of either physical or mental agility. In the case of atomic energy, the first two conditions were still only partially met: people did not fully understand atomic energy, and a number were not convinced that it would be of advantage to them individually. The third condition was not met at all. None of the human senses allowed a man to detect radiation and so alert his instincts for defence or flight, and it was that inability to escape by personal effort that led to the present exaggerated and disproportionate fear of all things nuclear. That was borne out by the fact that when the accident occurred at Windscale in October, 1957, the people who were the least alarmed were the men working on the job. While they knew that they could not by their unaided senses alert themselves to protective action, they saw all the health monitoring services in action and knew that these technical aids were supplementing their senses, and that gave them confidence.

If it were the case that risk was objectionable only when it led to protracted fear, and that fear only developed when there was failure to meet the three conditions he had enunciated, then, said Sir Christopher Hinton, surely that gave in industry, in industrial medicine, and perhaps in medicine generally a principle of great importance. In industry, staff and labour management should—and in well-managed industries did—aim not merely to provide good instruction and fair remuneration (their first two conditions), but also to make every individual feel that in the last resort the management would provide a way out for him if conditions became intolerable. In modern management they had learnt to rely on the advice of industrial medical officers to ensure that this condition was met. "The thought I should like to leave with you," concluded Sir Christopher, "is that if management fails to provide that way of escape it is often only the man's doctor who can provide the way out. At the same time, in industry the men who do not get the benefit of labour management are the top executives, and they usually can only rely on the doctor to open up a way of escape for them when a way of escape becomes really necessary."

ST. GEORGE'S HOSPITAL

Sir Claude Frankau, speaking at the inaugural ceremony of St. George's Hospital Medical School on October 3, contrasted present-day conditions and facilities with those which existed when he first entered the hospital as a student 57 years ago. Then the operating theatres had only recently been opened, and frock-coats were the order of the day. Indeed, a suggestion had recently been made that a proper form of professional dress at hospitals ought to be established. "In Wimpole Street or Harley Street," said Sir Claude, "you will see an extraordinarily scruffy lot of people. If the London consultants as a whole were properly garbed they would acquire greater prestige with the public than they have if they come in scruffy old tweeds."

When completed, the medical school would compare favourably with any school in London. "You will have to

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learn a great deal more than we did," Sir Claude told the students. But he implored them not to fly to the ancillary diagnostic services before trying to arrive at a conclusion themselves. They should use those services to confirm or refute their findings, and in that way they would really begin to learn.

Integration of Curriculum and Examinations

Dr. M. I. A. HUNTER, the dean, in his report said there was need for some form of integration to give cohesion to what the student learned, but that integration must be supported in the examinations. It was a responsibility for all teachers and medical faculties, and it was a particularly difficult problem in London, where students were examined by teachers from 12 different clinical schools. In the clinical period the patient should be the focal point at which the academic and the vocational aspects of medicine converged. There the detailed analysis of the laboratory fell into place against the broader background of the patient's personality as scientist, clinician, nurses, almoners, and—he would like to think—the patient's family doctor brought their particular skills into operation. Dr. Hugh Gainsborough* had recently suggested that that kind of teaching was essentially the duty of the general departments and provided the antidote to the fragmentation which could result from too much departmental teaching, valuable and stimulating though that was.

At St. George's Hospital Medical School they had already begun to teach in that way—it was essentially an extension of their traditional emphasis on bedside teaching—but he looked forward to its expansion as an educational method and as a contribution which might help to bridge the gap which separated the care of the patient in hospital from that in his own home. Dr. Hunter suggested that it was time that some institution had the vision to fashion a proper faculty of medical science closely based on human biology. A preclinical school with such a concept in mind had been projected at St. George's, but money had been scarce and the moment had passed. In America experiments of that kind at Western Reserve University† and elsewhere had been universally stimulating and had given a new impetus to medical study, but in this country, except perhaps at Birmingham University, nothing of the kind had been attempted.

*See his letter (*Journal*, September 27, p. 795).
†See *Journal*, October 4, p. 851.

Motoring News

THE MOTOR SHOW

Once again the Motor Show time has come around, and is to take place at Earls Court between October 22 and November 1, during which time the cream of the world's automobiles will be exhibited. Already some of the larger concerns have announced their new models, but a few will wait until the eve of the show to create a last-minute surprise. The tendency to-day is to spread out the announcement of new models over the year, for too many new models have become lost, in previous years, in the welter of publicity which the show receives.

One of the most important small cars announced recently was the new Austin A40. Using the well-tried A35 power unit in an Italian-styled body, the British Motor Corporation has added yet another car to its comprehensive range. At long last we are seeing the demise of the exterior luggage boot in favour of an all-enveloping body at the rear, with passengers and luggage under one roof. This is one of the best features of this A40, which sells for £676. I wonder how long it will be before manufacturers advance in the other direction to enclose the bonnet and dispose of the engine under the floor.

From Rootes Group comes the news that the Singer Gazelle will have more luxury, and the estate car on the same chassis will cost £45 less, bringing it into line with the Gazelle Convertible at £998 17s. A range of new colours, with coloured hoods to match on the convertible, now become available, together with improved seating and arm rests. The latest Hillmans will be exhibited with the recently announced 1,494 c.c. engine instead of the 1,390 c.c. unit, which is still being fitted to the Husky. The saloons, with this new 52 b.h.p. power unit and new rear axle ratio (4.55:1), are capable of 80 m.p.h., although prices remain unchanged. Many small detail changes have been made in the saloons and convertibles, such as restyled front grilles, two-tone colour schemes, improved instrument panel, and more comfortable seating. The special saloon, which is the cut-price model, has the performance improvements of the de-luxe models, but only has improved seats and radiator grille for the coming year. In fact, for those who seek a moderately priced family car with as much luxury as is necessary, the Hillman Special, at £748, is a good buy. The floor-change gear lever, rubber mat flooring, and single-tone colour scheme are not unpleasant features in any way; they even have advantages, for one can add more frills, if they seem desirable, at a later date.

Preliminary details about the Ford range indicate no major changes, but it is likely that the Anglia and Prefect models will have not only a face-lift but some major mechanical changes, if not at the show then at some time before next summer. The larger models, combining speed with luxury, are unlikely to be superseded at present. The Rover company have added to their range with the recently announced 3-litre model, a faster and more ostentatious-looking six-seater designed to cater for the luxury market as did the well-known "Twenty," made by this firm in pre-war days.

More and more models are appearing each year with overdrives, manumatic two-pedal control, and fully automatic transmission, and this year's show will see these features on more of the cheaper models. Many of these small cars now have some form of clutchless motoring available at a higher price, but as such methods of transmission are perfected they will gradually creep into production models at no extra cost, and the buyer who is willing to bide his time will reap the reward in the end. There is no reason why automatic transmission should not be achieved at small expense on low-cost models. Even the French 2CV Citroen, a cheap car if ever there was one, has a centrifugal clutch, but the British conservative design and vast mass-production set-ups preclude rapid change-over to novel features which are now proving their worth. A feature which is making a name for itself, however, is the disk brake, a British invention which is helping our sports car sales abroad immensely. The disk brake has many advantages over normal drum brakes, and the two major concerns which have been working on its development for some years are Lockheed and Dunlop. At present brakes of this type are reserved for sports cars because of their need for brakes which are powerful and, in particular, free of fade at high speeds. Soon, however, they will appear on sports saloons, and in less than a decade they will probably be standard equipment on the cheapest family cars.

Colour schemes for 1958–9 are likely to be altered, with more accent on dual colours and ornamental chrome. Interiors will offer more comfort with arm rests, and larger windows in some of the sports saloons will admit more light. Convertibles will still be scarce and, of course, expensive, but the dual-purpose type of vehicle will become even more popular especially in the lower-priced economy group. There still seems to be no hope of the sliding roof returning for those who crave small quantities of fresh air and sunlight. The tubeless tyre is here to stay, though no one has yet seen fit to throw away the spare wheel when these allegedly invincible covers are fitted.

Anything may happen in the ultra-small runabout classes, but it seems unlikely that such a model will be exhibited at a sensible price by a big concern with a view to mass production. Until this happens the miniature car cannot

(*Continued at foot of next page*)

To-day's Drugs

Vasculit (Pfizer Ltd.).—This is the sulphate of 1-(*p*-hydroxyphenyl) - 1 - hydroxy - 2 - *n* - butylaminoethane, which is the N-butyl homologue of oxedrine. The principal effect of this drug is to cause peripheral vasodilatation; it has little effect on the blood pressure or the heart rate, though it increases the output of the heart per beat. It has been prescribed to increase the peripheral blood flow, but, though available for several years in Germany, it has so far been little used in Britain and America. It is supplied in tablets containing 12.5 mg., which are hygroscopic, and as drops (1%). Its action lasts for only two hours, and the dose, usually one tablet and not more than two (25 mg.) at a time, is repeated frequently, sometimes as often as every 2–3 hours. The amount required varies greatly in individual cases, older people usually requiring more. Doses which are too high may lead to vasoconstriction.

N.H.S. basic price: 50 tabs., 6s.; 1 fl. oz., 4s. 11d.

Cortico-Gel (Crookes Laboratories Ltd.)—This substance is corticotrophin in hydrolysed gelatin solution with tricresol 0.3%. It is put up in two strengths, 20 and 40 international units per ml. It is suitable for subcutaneous or intramuscular injection in doses of 10 to 60 units daily for all those conditions in which corticotrophin is indicated. Its distribution is restricted by the Ministry of Health to hospitals.

Episol (Crookes Laboratories Ltd.).—This is a 0.5% preparation of 5-chloro-2-(*p*-diethylaminoethoxyphenyl) benzthiazole as a lotion, cream, or dusting-powder. General considerations on the use of antiseptics in ringworm infections of the skin mentioned in the note on "epidexa" (October 11, p. 913) are also relevant with episol. Benzthiazole may cause high degrees of sensitization when handled—as, for example, in the rubber industry. This does not necessarily mean that the benzthiazole derivative used here as an antiseptic will have a similar sensitizing potential, but it indicates the need for caution.

The makers recommend continuing to apply the powder after clinical cure, presumably intending that treatment should be continued for a considerable period. This would seem to be a practice of doubtful wisdom, particularly since the product is a new one and sufficient time has not yet elapsed for its sensitizing potential to be adequately known.

N.H.S. basic price: 4s. 8d. for 30 ml. of lotion, 30 g. of cream, or 30 g. of powder.

(*Continued from previous page*)

compete on equal terms with the lowest-priced full-sized model at present on the market. The German "bubble" cars can do this by quantity manufacture and still sell their products in Great Britain after paying import duties.

In general, then, it appears that 1958–9 will be a year of general improvement in mechanical aspects, with more power and more speed achieved by good design so as to give maximum economy, for manufacturers to-day are very conscious of m.p.g. figures. Body styling will give more space and more leg room in present designs, while new models will concentrate on full width seating and larger luggage compartments and, it is to be hoped, better engine accessibility. Any new models for the coming season will be introduced between now and February next year, but for the next few weeks Earls Court will attract the thousands of buyers as well as the thousands of lookers-on who are interested in viewing their future second-hand or even tenth-hand cars. But as probably the greatest motor exhibition on earth there is sure to be a car to suit every possible kind of buyer provided he or she can afford it; we can only hope that for some of us there will be the right model at the right price.

IAIN GELLATLY.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Coloured Immigrants

SIR,—I have been in general practice in Notting Hill for five years, and have a fairly intimate knowledge of the recent pogrom, which presumably is the occasion for your annotation on coloured migrants (*Journal*, October 4, p. 843). Those doctors who work in areas with coloured minorities are faced with an outbreak of a serious epidemic disease, which we had imagined to be confined to less civilized countries. It would certainly be an opportune moment for the leading journal of the profession to restate those humane and scientific principles which contradict every manifestation of racial mysticism. Instead I was astonished to read that "All would agree with the (Eugenic) society's advocacy of more research into the results of race-mixing." I certainly do *not* agree, and I hope there are very few others in the profession who will; I should have thought rather that the hysterical behaviour of an English mob throwing burning bottles of petrol into the living-rooms of perfectly decent families who simply happened to differ from them in the colour of their skin would be a more worthy and opportune subject of research. The subject of miscegenation would already appear to have been thoroughly investigated by the race-scientists of Germany and South Africa.

I hope, Sir, that you will soon devote some space to a serious study of this potentially very serious problem, in an article more worthy of our traditions.—I am, etc.,

London, W.11. J. TUDOR-HART.

Attempted Suicide

SIR,—It is good to read in Dr. A. A. Bartholomew's important letter (*Journal*, September 20, p. 740) that the prospect of psychiatric treatment in the prison setting seems less forbidding from the inside than it is from without. However, he fails to convince me that the law on suicide should remain. I wonder if he is over-emphasizing the number of cases that need compulsory treatment but which are not admitted by the duly authorized officer. After all, he does not state, of his own cases, that they were refused—perhaps the officer was not called. Where a patient intends a further suicidal attempt I have never known an officer not to act, however normal the patient may have otherwise been. The experienced officer seems remarkably well able to judge which patients need compulsory treatment, and the proposed addition of one or two medical recommendations[1] would make the procedure even more cast-iron.

Again, conceding that exceptionally there may be suicidal patients better handled by the punitive services (and Dr. Bartholomew has not proved this), is it right that a few hard cases should justify a law which bears so unpleasantly upon such a vast number? We are told that hard cases make bad law. There are various other laws under which difficult though not certifiable behaviour can be tackled—indeed, this *Journal* really settled the matter when it said[2] that the Scottish practice should be adopted. It might not be so bad if Dr. Bartholomew and others with special training in mental disease administered the law, but our judicial colleagues, whatever their other inestimable qualities, are not the best people to decide which patients need what kinds of treatment where. Professor Glanville Williams[3] has given ample evidence of this in his figures for 1955 that, of 5,220 attempted suicides known to the police (less than a seventh of the total, according to Professor E. Stengel[4]), only 43 were imprisoned; of these there was one sentence of *four* years and another of about two (it was not clear from the statistics), two others were *fined*, and four detained in a prison cell (probably for a day).

Asking what criteria of selection were used for this small minority, Williams wonders if there are principles other than the idiosyncrasy of judge or magistrate. One does indeed wonder.

If the abolition of the law were a revolutionary and experimental move, there would be better grounds for bringing in the modified reforms for which Dr. Bartholomew argues so cogently. As, however, we are way behind most other countries in this respect (France, for example, abolished the law in 1790) we should surely venture something a bit more definite. It has been said[5] that to incarcerate the mentally ill in prison is the very worst way of bringing about the social rehabilitation that such cases need. Surely it is not hard to agree with that.—I am, etc.,

London, S.E.5. RICHARD FOX.

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Exophthalmos in Cushing's Syndrome

SIR,—I read with great interest the paper by Drs. D. Crooke Morgan and A. Stuart Mason on "Exophthalmos in Cushing's Syndrome" (*Journal*, August 23, p. 481), and should like to congratulate the authors for reporting this unusual case. There are, however, certain points on which I should like to comment. Drs. Morgan and Mason state that "all the evidence (concerning the pathological physiology of exophthalmos) points to a pituitary-thyroid relationship." Is that really the case? In my monograph on "Exophthalmos: Its Relation to Adrenocortical Function"[1] I have pointed out that a disturbance of the pituitary-thyroid axis alone is not sufficient to explain some of the most interesting features of the clinical and experimental picture of exophthalmos. From 1941 onwards, when Friedgood[2] realized that ". . . another factor (than thyrotrophic hormone) must be responsible for exophthalmos," repeated attempts have been made to overcome this difficulty either by postulating a separate exophthalmos-producing factor of the pituitary or by endowing the orbital connective tissues with an increased sensitivity to the thyrotrophic hormone, or by postulating a failure of the thyroid gland to inactivate this hormone, etc. I must leave it to Drs. Morgan and Mason to fit their case into the strait-jacket of the theory of a disturbed pituitary-thyroid relationship, but I should like to ask why, in view of the fact that in their own case they could not present any clinical or histological evidence in favour of a disturbance of the thyroid gland, they should be so reluctant to invoke the alternative explanation which suggests itself in the light of my experimental findings on the part played by corticotrophin and the adrenocortical steroids in the production of exophthalmos.

Drs. Morgan and Mason state that I have produced an apparent exophthalmos in the experimental animal by cortisone. The notion of "apparent" as opposed to real exophthalmos has been introduced by Boas and Scow[3] to explain their findings in rats treated for prolonged periods with cortisone. Since Drs. Morgan and Mason quote my preliminary experiments in the guinea-pig,[4] I must call their attention to the fact that I have actually measured the increase in the intercorneal distance of these guinea-pigs, and that I find it difficult to reconcile the increase found with the notion of "apparent" exophthalmos. These experiments are reported in detail in the monograph which I have quoted above and which appears to have escaped the attention of Drs. Morgan and Mason. Ocular measurements in the rat are more difficult to obtain. Since I had not taken any such measurements in my experiments on exophthalmos in the rat, I did not feel justified in taking issue with the concept proposed by Boas and Scow, but I should now like to offer these comments:

(1) Experimental exophthalmos can be produced with great rapidity. In the guinea-pig treated with thyrotrophic hormone and cortisone a measurable increase in the intercorneal distance can be demonstrated within a matter of hours.[1] In rats treated with cortisone "real" or "apparent" ocular protrusion is noted within a matter of days.[5] Boas and Scow, who maintain that the inhibition of body growth, but not of eyeball growth, is the cause of the exophthalmic appearance of rats treated with cortisone, studied only animals that had been treated for a much longer period, when perhaps additional effects of cortisone complicated the picture.

(2) I have produced exophthalmos also in mature rats treated with cortisol,[6] but since the rat continues to grow for some time I should not like to stress this point unduly at the present time.

(3) Hypophysectomy produces inhibition of body growth with little or no inhibition of the growth of the eyeballs, yet exophthalmos has not been described in the hypophysectomized animal; cortisone aggravates the inhibition of the body growth in these rats, and leads to a highly significant increase in the relative eyeball weight, yet exophthalmos still cannot be produced.[7 8]

(4) Although the body growth of normal rats can be inhibited by restricted feeding to the extent shown by rats treated with cortisone, I have not been able to produce exophthalmos that way.

(5) Boas and Scow[3] have suggested that deficient diets, by inhibiting bodily development, possibly might produce a picture similar to that seen after the administration of cortisone. Rats fed a diet containing yeast as the only source of protein invariably develop liver necrosis, which is significantly delayed by the administration of cortisone. In animals fed the deficient diet only, I have never observed exophthalmos, although they showed approximately the same degree of inhibition of body growth (as measured by body weight) as their litter mates treated with cortisone as well; in these rats, however, exophthalmos was the rule. With the sudden onset of liver necrosis an established exophthalmos can disappear—although the relation of eyeball size to volume of orbit or body size obviously cannot be affected by this process.

(6) Cortisone appears to produce exophthalmos in intact or thyroidectomized animals only if it is given in a certain optimal dosage. If the amount is increased 3–5 fold, exophthalmos does not develop despite the much greater inhibition of body growth. In contrast to the animals treated with the lower doses these rats appear sick. If ocular protrusion was a matter merely of disproportion between eyeball and orbit, this factor should not enter. I suggest, incidentally, that this difference in the response to varying amounts of cortisone given could find a parallel in the fact that only a certain percentage of cases of Cushing's syndrome develop exophthalmos.

It must be apparent from these facts that disproportionate growth of the eyeballs under the influence of cortisone does not satisfactorily explain all the phenomena I have described. The case reported by Drs. Morgan and Mason, in my opinion, presents additional support for my thesis that the adrenocortical secretion is an important factor in the production of exophthalmos. I have, incidentally, nowhere stated that the adrenal cortex was at fault, but I have postulated a pituitary disturbance involving also the secretion of A.C.T.H.[1] This does not rule out a possible hypothalamic effect. Finally, I should like to draw the attention of Drs. Morgan and Mason to the fact that, contrary to their statement, in three cases of the series conducted by the Medical Research Council[9] ocular protrusion did increase during treatment with cortisone. Zondek and Ticho[10] and Woods[11] have also reported a similar effect.—I am, etc.,

Halifax, Nova Scotia. K. ATERMAN.

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Miners' Nystagmus

SIR,—In your leading article "Emotions and Miners' Nystagmus" (*Journal*, September 20, p. 732) you refer to the recent study I made of this disease using a battery of objective tests of emotional stability.[1] You point out that no information was given as to whether oscillations were present in the men suffering from nystagmus. I have analysed the case histories of these 67 men and find that

at the time of certification 42 men exhibited oscillations and 25 did not.

However, to test your hypothesis that men without oscillations are more likely to be certified on the basis of psychoneurotic symptoms I have compared the scores of these two groups on the four tests which discriminated in the battery. The Table shows that there was no significant difference

Test	Mean Score		t	p	Level of Significance
	Men with Oscillations	Men without Oscillations			
Heron I ..	10·00	9·00	1·26	p=0·2	Not significant
Food aversions	5·88	5·80	0·09	p>0·9	,,
Hand persistence	4·17	4·00	0·28	p=0·8	,,
Leg ,, ..	3·21	3·60	1·20	p=0·2	,,

between the men with oscillations and those without on any of the tests. In Heron I, the mean score of the men with oscillations was in fact higher (more neurotic) than that of the men without. Any suggestion, therefore, that the differences obtained in my study between the men with nystagmus and the controls were due to the men without oscillations being more neurotic is unlikely. In this study the severity of the disease was assessed from the symptoms and time the men had been off work before certification.—I am, etc.,

Newcastle upon Tyne, 1. JUDITH S. LION.

REFERENCE

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Nursing in Maternity Hospitals

SIR,—During the past 10 years of the National Health Service there has been a steady increase in the number of confinements in hospitals. Surely the time has come for a review of the standards of nursing in the maternity hospitals. I have recently met several mothers who have been very dissatisfied with their treatment and would in future prefer to be confined at home.

Some of the complaints—and the ones listed are restricted to those from mothers who are also State-registered nurses—are as follows: (1) Irregularity of swabbing after delivery. In one case the patient was left for hours before any action was taken. (2) Issuing of medicines other than those prescribed and continuing to issue after the prescription had been discontinued. (3) Allowing cleaners and other untrained staff to feed babies. (4) Incorrect use of intramuscular iron. In one case the patient was given injections at intervals between the knee and buttock and now several months later has severe aching of the leg.

Many of these complaints are the result of overwork and wards being understaffed, but the conditions should be borne in mind by general practitioners who refer patients for hospital confinement. I might add that I am not referring to our local maternity hospital in my remarks.—I am, etc.,

Goodmayes, Essex. J. A. HOLLAND.

Pathogenesis of Fever

SIR,—On reading your leading article concerning the pathogenesis of fever (*Journal*, October 4, p. 839) I noted a plea that some of the experimental work should be repeated on a species other than the rabbit. This has in fact been done in man,[1 2] and the evidence adduced for the formation of endogenous pyrogen from an interaction between leucocytes and bacterial pyrogen is impressive. In man the reduction in the latent period between the injection of material and the onset of fever is very much shorter for endogenous pyrogen than for bacterial polysaccharide. This contrasts with the rabbit, where the shortening of the latent period is much less obvious.

One might gain the impression from your leading article that the leucocyte was the only blood element which could interact with bacterial pyrogen to produce endogenous pyrogen in the rabbit. Bacterial lipopolysaccharide after incubation for three hours at 37° C. with cell-free rabbit plasma produces a substance with properties in common with endogenous pyrogen—namely, heat lability and inability to produce tolerance on repeated intravenous injection.—I am, etc.,

Oxford. K. E. COOPER.

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Tonsillectomy and Poliomyelitis

SIR,—I was very interested in the cases of poliomyelitis quoted by Dr. A. B. Christie in the *Journal* of October 4 (p. 855). He recommends a postponement of tonsillectomy until after inoculation. But why operate at all in the average case? Those of us working in the field of infectious disease do not protest when the introduction of each new prophylactic means a further reduction in our activities. Surely our ear, nose, and throat colleagues should show an equal enthusiasm by conscientiously and scientifically analysing their indications for this operation and their follow-up results. The fact that something of the order of 250,000 tonsil operations are done annually here should not make this difficult. Recent studies have shown the dangers of this operation not only in poliomyelitis but in streptococcal and other infections. The fact that any operation is commonly performed does not necessarily imply that its indications are right.—I am, etc.,

Romford, Essex I. M. LIBRACH.

Dinitrophenol and Diabetes Mellitus

SIR,—Although little experimental work has been done with 2:4-dinitrophenol (D.N.P.) in humans before that reported by Dr. James Reid (*Journal*, September 20, p. 724), some results on experimental animals were obtained earlier concerning the effect of this drug on carbohydrate metabolism.[1 2] D.N.P. exerts a remarkable hyperglycaemic effect in intact dogs, while a small decrease of the blood sugar level can be observed in pancreatectomized animals. The increase in oxygen consumption, hind-leg blood flow, and blood lactic-acid level was the same in the two groups of animals, but the serum inorganic-phosphorus level showed a much higher increase in the diabetic dogs. We have found a diminished glucose uptake by the muscles of the diabetic dogs *in vivo*; the blood sugar level has shown nevertheless the above-mentioned small decrease.[2] This difference in the action of D.N.P. is similar to the variable effect of salicylate mentioned by Dr. Reid. It may be explained probably by considering the different glycogen levels of the liver in the normal and diabetic dogs.—I am, etc.,

Szeged, Hungary. M. WINTER.

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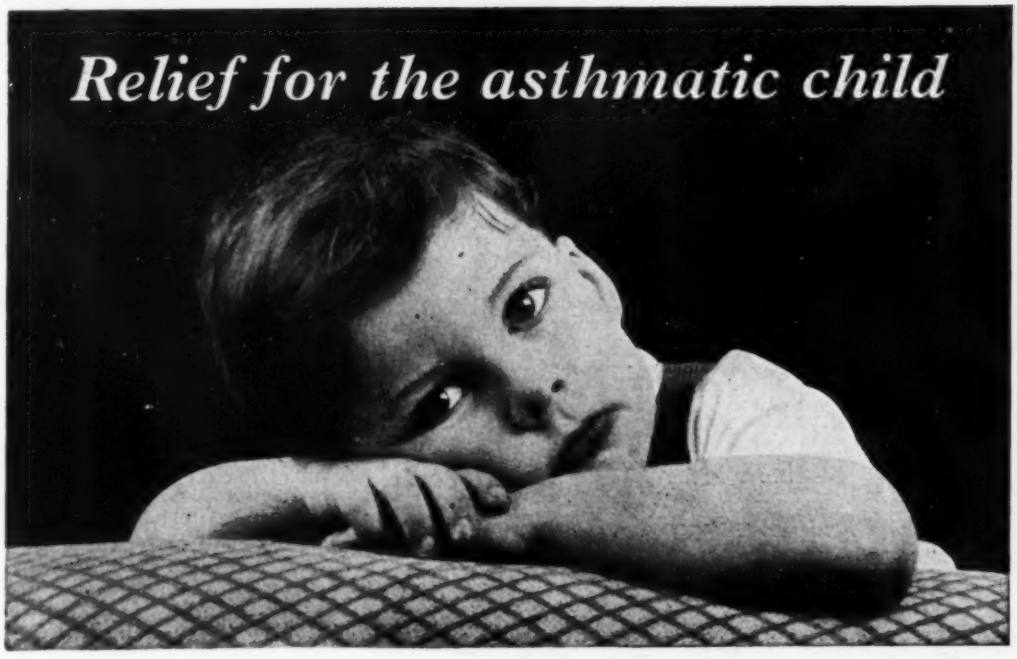
Mass Casualties and Nuclear Warfare

SIR,—I am very much aware of the excellent work being done by the "One-in-Five" scheme of the W.V.S. (*Journal*, September 27, p. 799), but until the Government gives more publicity to the subject of Civil Defence and its importance those responsible for such education find great difficulty in engendering enthusiasm. The subject is looked upon as political dynamite when it should be regarded as a completely non-political issue.

I am greatly indebted to Dr. M. C. Berenbaum (*Journal*, September 27, p. 800) for drawing my attention to an arithmetical error reproduced in my paper (*Journal*, August 9, p. 379) from the original source quoted. I am not, however, even slightly repentant for being "irresponsible" enough to suggest certain measures that could reduce the misery, panic, and chaos which I agree must follow resort to nuclear warfare. To correct the mistake in the figures I quoted, I have recast the figures on the basis of two minutes for sorting and 8–9 minutes for life-saving operations—



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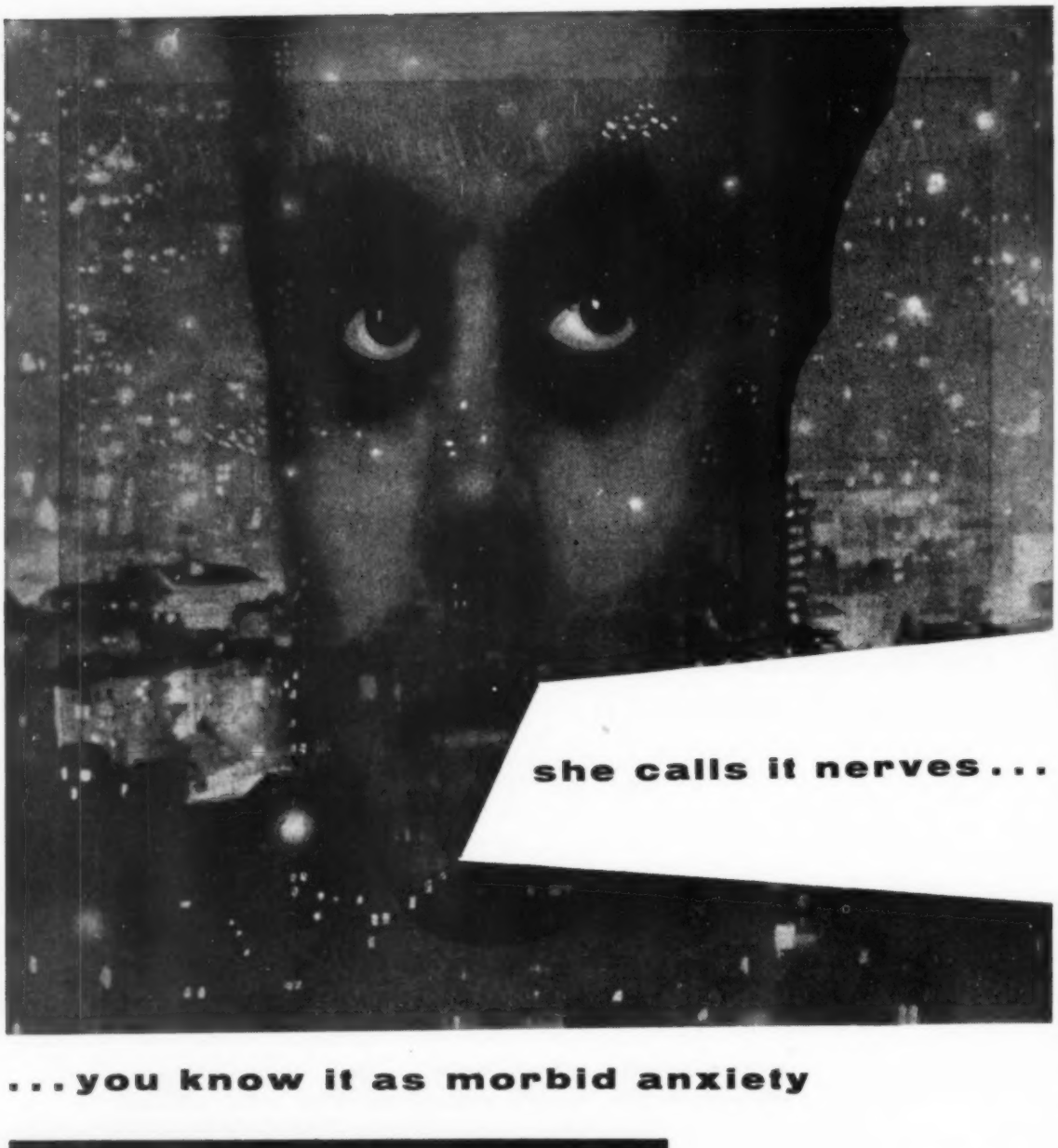

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control of haemorrhage and attention to the airway, and urgent amputations. This would allow three teams of eight doctors—the number in two F.M.A.U.s—working two eight-hour shifts in the 24 hours to sort seven thousand casualties and carry out the 1,200 urgent medical procedures suggested, provided there were the necessary nursing, first-aid, and unskilled staff for porterage and policing available. Of course this pressure of work would only be for a very limited period. In a recent exercise held in the South-West Region, the time required for sorting was found to be considerably less than two minutes per individual.

Dr. Berenbaum's view that there will be no inkling that war is imminent until the nuclear weapons are in the air on their way to their target does not of course agree with the belief of all those who have been studying this problem for the last ten years. With regard to "fall-out," this problem is recognized only too well and alternative hospital areas have to be planned on account of this. A second nuclear weapon on the same target is, however, extremely unlikely, and it seems unnecessary to make a very difficult problem even more so by expecting the grossly improbable.

I will conclude with the final remark from the report on "Exercise Reliance" held this summer in the South-West Region, which after careful analysis and criticism by the planning committee finishes: "The exercise has proved that effective planning and training, coupled with good will on the part of all the Services concerned, would be able very considerably to mitigate the effect of such a disaster."—I am, etc.,

Bath, Somerset. G. D. KERSLEY.

Antenatal Irradiation and Childhood Malignancies

SIR,—Dr. J. Rabinowitch's letter (*Journal*, September 27, p. 796) puts forward two main contentions: first, that the publication of our preliminary report[1] was followed by an exaggerated reaction against antenatal radiography; and, second, that the conclusions of that report, recently reaffirmed,[2] are in any case not valid. The first of these contentions amounts to a criticism of those among his colleagues who have "severely curtailed" the number of their antenatal *x*-ray examinations. We are most anxious not to take either side in this dispute, but feel obliged to point out that the argument presented is a heavily loaded one. It ignores the genetic risks associated with irradiation of the gonads, to which antenatal *x*-rays make a disproportionately large contribution.[3] Increasing consciousness of these risks must have weighed quite as heavily with radiologists as any inferences drawn from our work. Having chosen to concentrate exclusively on the somatic risks, Dr. Rabinowitch (in our view) understates these also. His absolute risk of 1 in 3,000 purports to come from our paper ("If their results were accepted it would mean . . . ") but is in fact his own figure, arrived at by an unstated method, and is less than half our own, very tentative, estimate. Moreover, the risk assumed by him would yield as few as "between 20 and 30" deaths per year *only if* the proportion of foetuses irradiated is kept down to about 1 in 10. Routine pelvimetry of primiparae, which has sometimes been advocated, could quadruple the expected number of casualties.

In his attack upon the validity of our findings Dr. Rabinowitch aims to show that we "have not paid enough attention to the various groups of maternal characteristics which differ widely in their respective numbers in the case and control groups and which may constitute an increased indication for the taking of radiographs." He claims that, when proper allowance is made for these differences, the whole of the apparent difference between cases and controls in respect of foetal irradiation can be explained away. (It is an unspoken assumption of this argument that such maternal characteristics *do* affect the likelihood of childhood cancer.)

As his starting point, Dr. Rabinowitch chooses the figures of our Table VII in which the number of irradiated cases exceeds the corresponding number of controls by only 60. Now, as the title and surrounding text clearly state, the figures in this Table do *not* show the full observed difference between our case and control groups: they are the basis of a hypothetical comparison in which we attempted to discount for various possible sources of bias. In particular, these figures exclude *all* *x*-ray exposures associated with maternal ill-health. It follows that Dr. Rabinowitch's remarks about maternal illness (his paragraph (3))—themselves a selected and partial account of the evidence—are irrelevant.

The relative frequency of antenatal *x*-rays reported for first and later pregnancies (our Table IV) is so different from Dr. Rabinowitch's expectation that he feels entitled (see his paragraph (1)) to apply an *a priori* adjustment to the figures. This takes the form of multiplying the reported frequency of examinations among control primiparae by 1.6 while leaving the reported frequency on the case side as it stands. The unstated assumption on which this procedure rests may be worded as follows: If case mothers are x times as efficient as control mothers at reporting the events of third and later pregnancies, then they are 1.6x times as efficient at reporting the events of first pregnancies. Our assumption was that the relative reporting efficiency of case and control mothers would be the same for events of all pregnancies. This has the merit of being simple and also of fitting the facts, which his more complicated assumption does not. Incidentally, even if his suggested adjustment were applicable it would involve a total addition of 22 cases on the control side of which perhaps 18 (not, as stated, 33) would fall within the scope of Table VII, reducing the case/control difference in that Table to 43 (not, as stated, "under 30").

Dr. Rabinowitch has assumed (his paragraph (2)) that there was a surplus in our case series of 30 women who were aged 40 or over at the time of the relevant pregnancy. The correct figure (which we would have been pleased to give him) is 2. As a whole, the mothers of the case group were significantly *younger* than their controls, so that our survey was, in this respect, biased *against* the discovery of any association between foetal irradiation and later malignancy.

Dr. Rabinowitch says (his paragraph (4)) that there was an excess of 37 case-mothers with a past history of abortion and of seven with a past history of stillbirth. Here he has again failed to read the title of the Table from which he is quoting (number XXIV) which explains that the figures go up to the date of the survey child's death. We are not able to say how much lower the figure for *past* histories of abortion and stillbirth would have been. However, the exact number is of no interest, since, contrary to Dr. Rabinowitch's assumption, these women were *not* more frequently *x*-rayed than others. (Perhaps they *should* have been, but that is another matter.)

Thus the alleged "excess of 122 anomalous mothers in the case group" shrinks to a maximum of 2. Two further points: (i) Even if there *were* an excess among the case-mothers of "anomalous types" it would be quite wrong to impute abdominal *x*-rays to a "balancing" group on the control side at the arbitrarily suggested rate of one in four. This is far higher than the rate actually recorded among the "anomalous" mothers in the case series. (ii) In any such balancing procedure the number of radiation histories on the control side should be increased not by the full assumed incidence among the imaginary controls but only by the margin by which this exceeds the recorded incidence among the actual controls.—We are, etc.,

J. W. WEBB.
DAVID HEWITT.

Oxford.

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Treatment of Bell's Palsy

SIR,—I have been interested to read the paper by Mrs. J. Mosforth and Dr. D. Taverner (*Journal*, September 13, p. 675), and would like to make some further observations upon the treatment of Bell's palsy. In a survey of the treatment of some 50 cases which I have carried out over the past two years there emerges a definite segregation of the cases into two distinct groups: (1) those in which the paralysis is of a transitory nature, the condition clearing up within four to six weeks with little or no treatment; and (2) those where the paralysis is profound, with severe epiphora, and in which there is a prolonged resistance to treatment.

Further investigation of the two groups shows that the former is usually confined to those who have a normal dentition or are wearing dentures which give a normal vertical dimension of the bite. All cases of the second group, which have needed prolonged treatment, have been found

to be without posterior teeth; or to be wearing dentures with a markedly closed bite—that is, owing to alveolar absorption the upper denture has "sunk" upwards and the lower downwards. Thus the jaw closes considerably more than when natural teeth are present, causing an abnormal rotation and backward movement of the condyle. It is suggested, therefore, that if the exciting cause of Bell's palsy occurs where a normal height of the bite is present (group 1) the paralysis will be transitory and will respond quickly. If this same exciting cause occurs where there is a closed bite, a predisposing condition exists, and the attack will be severe and prolonged, resisting treatment.

In the cases in group 2 the following treatment is now adopted as routine:

(1) During the acute stage: (*a*) Application of warmth, gentle massage, and in some cases short-wave diathermy to relieve pain. (*b*) Eye-shield to relieve pain and for the psychological benefit resulting from the cosmetic improvement. (*c*) Explanation of cause. Patients are usually distressed, often thinking that they have had a "stroke."

(2) An effort to restore function and to prevent fibrosis of the muscles: galvanism (for what it is worth) and massage.

(3) New dentures should be constructed with an opening of the bite not less than 5 mm.—more if this can be tolerated by the patient and if the cosmetic result is not unfavourable.

(4) The attachment of an intra-oral lip support. This latter has the following advantages: (*a*) Tremendous psychological relief, since, with the face in repose, a normal appearance is restored. (*b*) Muscles are held in relaxed position. The old hook in the angle of the mouth, attached to the ear, pulls the orbicularis oris muscle out of position and can contribute to permanent disfigurement. (*c*) It is possible to watch the progress of the condition: as the muscle tone returns the lip becomes thinner and more retracted against the teeth, leaving the support more and more obvious at the corner of the mouth.

It is my opinion that the closed-bite syndrome may exist in many cases of Bell's palsy which hitherto have proved recalcitrant to treatment along the lines described by Mrs. Mosforth and Dr. Taverner. It is hoped to publish a more complete review of this subject in the near future.—I am, etc.,

Blackpool, S. JAMES BOOTH.

Fishbone Furunculosis

SIR,—I was interested to read Dr. Peter Cook's letter (*Journal*, September 27, p. 797) and wondered if the condition he described might be an atypical erysipeloid (Rosenbach). This condition is endemic among persons handling fish and has a strictly seasonal incidence[1] which varies closely with latitudes and the times of insect activity.[2] The condition is not so painful as true boils, and usually responds to penicillin. The *Staphylococcus aureus* may have been a secondary invader.

Boils on the hands and wrists of fishermen were regarded as "salt sores" in the past, and in the old days in the north-west of Scotland thick copper chain bracelets were used to prevent these. Presumably they stopped the friction of coarse oilskins on the skin.—I am, etc.,

London, W.1. IAN MARTIN-SCOTT.

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Obstetric Anaesthesia

SIR,—I have just administered the fiftieth anaesthetic for forceps delivery in the Worthing Group of Hospitals. Every time my first step was the intravenous injection of 25–50 mg. promethazine. On no occasion did regurgitation or aspiration of food and vomit occur. Once, in fact, during post-operative oxygen therapy, a patient at Southlands Hospital quietly removed the oral airway and asked for tea. A cup of tea was given to her immediately and this she retained comfortably.

Apropos of recent correspondence (*Journal*, August 23, p. 508) I submit this as a major consideration in any domiciliary obstetric operation requiring general anaesthesia. I have never adopted any special position or precaution such as laryngeal intubation in this series of forceps deliveries. All patients received nitrous oxide (a few thiopentone 250 mg.), minimal ether, gallamine 40 to 60 mg., and pethidine 50–100 mg. with the ergometrine at the time the baby (consistently crying) is delivered, a technique quite simple and suitable for the tyro. After advocating chlorpromazine and pethidine for premedication in the January issue of *British Medical Bulletin*,[1] Crawford later suggested[2] substituting promethazine for chlorpromazine in order to limit restlessness and hypotension, the two main toxic effects of the phenothiazine anti-emetic drugs. Pethidine given intraoperatively always prevents restlessness, while the danger of significant hypotension only becomes important in operations like caesarean section, which are outside the scope of domiciliary practice. Nevertheless, in the light of the work by Eckenhoff *et al.*[3] I always measure the blood pressure as frequently as possible, without having discovered significant falls in the fifty cases on which this communication is based.—I am, etc.,

Shoreham-by-Sea. J. W. MOSTERT.

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The Prescribed Diseases

SIR,—Your editorial review under the above title (*Journal*, October 4, p. 841) of a Report of the Industrial Injuries Advisory Council[1] states: "The report also acknowledges that primary neoplasm may occur not only in the bladder but also in the renal pelvis following exposure to aniline and some diphenyl compounds and certain derivatives of them."

If this statement were true it could only mean that the Advisory Council considers that workmen exposed to aniline are subject to an occupational risk of contracting a neoplasm of some part of the urinary tract. In fact, the Report does not mention aniline in this or any other connexion, and the prescription for Disease No. 39 (papilloma of the urinary bladder) does not cover exposure to aniline, nor is there any suggestion that it should do so.

Although the term "aniline tumours of the bladder" has been slavishly copied from textbook to textbook for a long time, modern authoritative opinion[2] based on an extensive survey in this country takes the view that "no evidence was found even to suggest that the manufacture or usage of aniline caused bladder tumours."

In these circumstances I consider it grossly irresponsible for the editor of a widely circulated journal when reporting the considered opinion of a statutory Advisory Committee to interpolate and gratuitously to inculpate as carcinogenic a substance very widely used in industry.—I am, etc.,

London, S.W.7. ROBERT A. M. CASE.

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*** We regret the error. The substances listed in the Report of the Industrial Injuries Advisory Council are as follows: "(i) Alpha-naphthylamine or beta-naphthylamine. (ii) Diphenyl substituted by at least one nitro or primary amino group or by at least one nitro and primary amino group. (iii) Any of the substances mentioned in sub-paragraph (ii) above if further ring substituted by halogeno, methyl or methoxy groups, but not by other groups. (iv) The salts of any of the substances mentioned in sub-paragraphs (i) to (iii) above. (v) Auramine or magenta." Exposure to auramine or magenta is limited for those purposes to exposure in manufacturing processes.—ED., *B.M.J.*

Informing the Hospital

SIR,—The letter from Dr. Biswarup Bhattacharya (*Journal*, September 6, p. 640) raises the question of identification of drugs. A doctor sending a patient into hospital may not forward details of current medication, as often the records are not available at the time the letter is written. Frequently an admission is arranged by a rota doctor or locumtenent, who has no knowledge of the patient's previous

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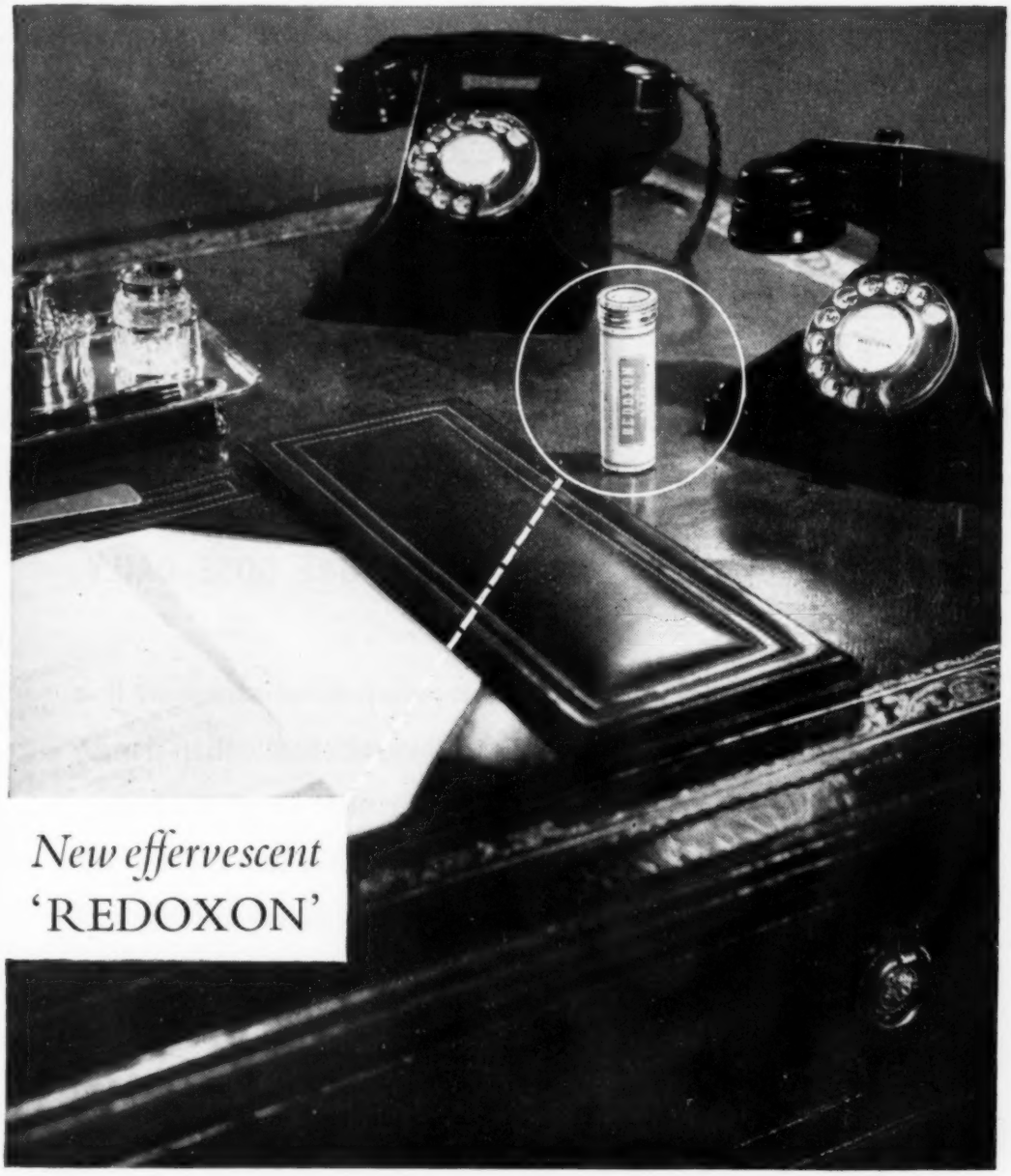

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medical history. In these instances the relatives may gather around with assorted boxes of what are usually plain white tablets and say, "I expect this will help you, Doctor; you will know what these are for." Little do they realize our plight.

I have made an identification box which is based on the one that Drs. Brian Russell and N. A. Thorne introduced to the Skin Department of the London Hospital. I have found it particularly useful for out-patient psychiatric clinic practice when I attempt to discover the previous medication. Because of the small number of drugs that can be identified, it is easy to fit the box into my jacket pocket. It holds 49 specimens and measures 5.5 in. × 4.75 in. × 1 in. (14 cm. × 12 cm. × 2.5 cm.). It is wooden and has a "perspex" lid. The identification key is on the reverse.

Perhaps one day some system of identification of drugs will be officially recommended by a body such as the Joint Formulary Committee, and then the Minister of Health will see this is brought about. In this way every doctor will be conversant with every patient's treatment.—I am, etc.,

London, E.8. NORMAN GOLD.

Halothane Concentration

SIR,—Drs. P. J. C. Burton and F. R. Gusterson (*Journal*, September 27, p. 799) write: "We are perturbed at the suggestion that an anaesthetist might be content these days to use an unknown concentration of halothane; surely we have reached a stage in the evolution of this anaesthetic agent that it is imperative to know that we are delivering continuously a safe concentration to the patient?"

Surely the safety of any inhalational anaesthetic agent lies in the fact that it must be given in test doses. By this means the minimum amount of the drug is given to maintain the level of anaesthesia required, and in my experience this involves frequent alteration in the concentration delivered. The continuous administration of a known so-called safe concentration may produce a sense of false security, as that which is a safe concentration for one patient may be lethal for another; a safe concentration at an early stage of an operation may amount to a gross overdose later on.

I suggest that careful observation of the patient's reactions to the drug provides a more than adequate substitute for accurate knowledge of the concentration being delivered, and I for one am not only content to administer an unknown concentration of halothane but would recommend it as a safer technique to teach junior anaesthetists than the continuous administration of a known concentration on the assumption that it is safe.—I am, etc.,

London, S.E.21. DAVID G. HURTER.

Petrol-vapour Poisoning

SIR,—Dr. Reed Aidan's article (*Journal*, August 9, p. 369) made very interesting reading. I, too, have been unable to find published accounts of death due to inhalation of petroleum vapour in any British medical publications. I have, however, had practical experience of two such cases, rare though they may be.

The first case was concerned with a tank dipper. This man had climbed to the top of a gasoline storage tank for the purpose of dipping, and for some unaccountable reason, instead of using the small orifice specially constructed for this purpose, he opened the larger adjoining cover: when found the individual lay alongside this open cover, quite dead. He was extremely cyanosed and his posture seemed to indicate that he had literally dropped in his tracks as though pole-axed.

The second case concerned a deckhand on a small coastal gasolene-carrying vessel; this vessel was being loaded when there was apparently a leakage of gasolene below decks. The individual concerned went down into the hold to investigate the leakage; after a considerable period, when it was decided that he had been in the hold too long, another member of the ship's crew entered the hold with suitable breathing equipment; the individual was found on the floor, quite dead. Extreme cyanosis was a feature of this case also.

The picture presented by acute gasolene poisoning is, of necessity, not a constant one. In the main, gasolene is a mixture of saturated straight chain hydrocarbons of the paraffin series, mostly ranging between pentane (C_5H_{12}) and octane (C_8H_{18}). In addition, unsaturated aliphatic hydrocarbons, i.e., olefines, di-olefines, and acetylene series triple bonds, may also be present, these latter in varying proportions. Additional chemicals are more often than not added in small quantities as inhibitors and anti-knock agents, e.g., tetra-ethyl lead, nitrobenzene. However, it should be remembered that cracked gasolene products contain a larger percentage of olefines and cyclic hydrocarbons—up to 40 to 50%, and, furthermore, aviation gasolenes are blended with benzene benzex (this latter a mixture of aromatic hydrocarbons), etc.

The lower homologues of the paraffin series can on acute exposure cause narcosis and death, the margin between the two being very small.[1] The aromatic hydrocarbons on acute exposure produce a neuro-irritation followed by death due to respiratory failure, although myocardial failure due to direct toxic action and also possible myocardial sensitization resulting in ventricular fibrillation and death can also occur.[2,3] The cyclo-paraffins and the olefines are capable of causing cardiac arrhythmias and vasodilatation. The olefines in addition have a strong anaesthetic action, amylene, for example, having been employed for surgical anaesthesia.

From the foregoing it can be seen that acute gasolene poisoning would present a composite picture, the predominant findings depending entirely on the composition of the inhaled product, which, as has been shown, can vary considerably.—I am, etc.,

Urmston, Manchester. B. GEORGE.

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Homosexuality

SIR,—In the *Journal* of October 4 (p. 837) your critic, Dr. Desmond Curran, dismissed in the space of one column over one thousand pages written on the subject of homosexuality. I have not read any of the books reviewed, although three out of the four authors are known to me through previous works, and I cannot therefore say anything about the matter of Dr. Curran's reporting. But about the manner I would like to say something. Let us certainly make the *Journal* interesting and attractive, but not by interspersing our critiques with ill-chosen asides levelled at the products of serious and dedicated minds. Destructive criticism is an easy achievement, from the Sixth Form upwards, and on this account should be submitted to thoughtful discipline and disciplined humility before launching it into print.

The final sentence in the column forms a curious climax to the whole. I may be quite ignorant on the ethics of scientific criticism, but am astounded to find that Dr. Curran was given the latitude to advertise a book of his own choice as a final buttress to his criticism of four books which had been handed to him by the *Journal* to read and report upon. The implication of this kind of critic's licence is clearly this: "Don't read or buy any of the books I have just told you about, because I know of a much better one. And here it is." One hesitates to speculate on what would happen if this sort of thing were to become a precedent in the *Journal's* review columns.—I am, etc.,

Kingswinford, Staffs. W. A. O'CONNOR.

Beds for the Aged

SIR,—In her letter (*Journal*, September 20, p. 741) Dr. Eluned Woodford-Williams gives some interesting figures concerning the geriatric admissions at Sunderland. I am in full agreement with the last paragraph of her letter, and no one wishes to return to the old pattern of gerontology when patients were left lying in bed for years and no rehabilitation attempted. Her statistics, however, make me wonder just what does happen in Sunderland to the

chronically confused, the frail, and the chronic sick patients so well known in all geriatric units. Could it be that these figures mean that these types of patients are not accepted in the Sunderland Geriatric Unit, and merely refer to acute medical admissions with a bias to the elderly patients?—I am, etc.,

Bradford, 5. K. M. Tankard.

International Society for Hypnosis

Sir,—In view of the past vicissitudes in the practice of hypnosis and its present revival, it may be of interest to your readers to know the latest organized developments in this field. On October 5 the International Society for Clinical and Experimental Hypnosis was inaugurated. This is a society which has branches in this country, the U.S.A., Argentine, Australia, Brazil, Canada, Chile, Denmark, Germany, Japan, the Netherlands, Norway, Sweden, and South Africa. Branches are also being formed in France and Italy at the present moment. The British Section of this society contains 124 members, and a journal, the *International Journal of Clinical and Experimental Hypnosis*, is published quarterly. The society consists of medical practitioners, dental practitioners, and psychologists, and is divided into fellows, members, and associate members. An American board of examiners in clinical hypnosis has been formed with medical, dental, and psychology divisions. This board is patterned after the other certification boards of the A.M.A.

As, for so long, the practice of hypnosis has been sporadic, and any real value it might have overlaid and distorted by exaggerated and wishful claims, which were rarely followed up, the formation of this group is a major step forward to allow hypnotism to take a reasonable place beside other therapies. The aims of the group, apart from teaching and the exchange of knowledge on the subject, will be greatly concerned with a scientific and non-prejudiced assessment of its true value. The preponderance on the board of directors of the society of many eminent experimental psychologists and psychiatrists from the major American hospitals should make this aim realizable.—I am, etc.,

A. A. Mason.
Secretary, British Division of the International Society for Clinical and Experimental Hypnosis.

37, Devonshire Place, London, W.1.

The Pharmaceutical Industry

Sir,—Your contributor, Dr. R. S. Inch (*Journal*, October 4, p. 846), is certainly not lacking in effort to put over propaganda for the drug manufacturers, but, in my opinion, he does not disclose all the facts but makes vague generalizations without providing any proof, and some of his arguments are contradictions. He infers that the use of more expensive drugs has reduced visits to the doctor, and then goes on to state that the increase in prescribing is due to the increased visits to the doctor. He also states that there has been a considerable decrease in number and duration of admissions to hospital, but produces no figures to prove his statement, which I gravely doubt. He states that future advances in therapeutics will reduce time lost from work.

Why talk vaguely about the future when the figures of drug costs and time lost due to sickness are available for the past ten years? An analysis on these lines would be of some value and even perhaps a guide to the future.—I am, etc.,

Doncaster. W. E. McPhillimy.

Prevention of Lung Cancer

Sir,—We not only admire Mr. Leslie J. Temple's courage (*Journal*, October 4, p. 858), but fully endorse his views regarding cigarette-smoking and lung cancer, and propose, in future, to follow the course he recommends. We suggest that in the appropriate case the death certificate should read as follows: "Cause of death: Carcinoma of lung or bronchus, due to cigarette-smoking."—We are, etc.,

Wilfred Lester.
Norman Macdonald.

London, N.W.1.

Obituary

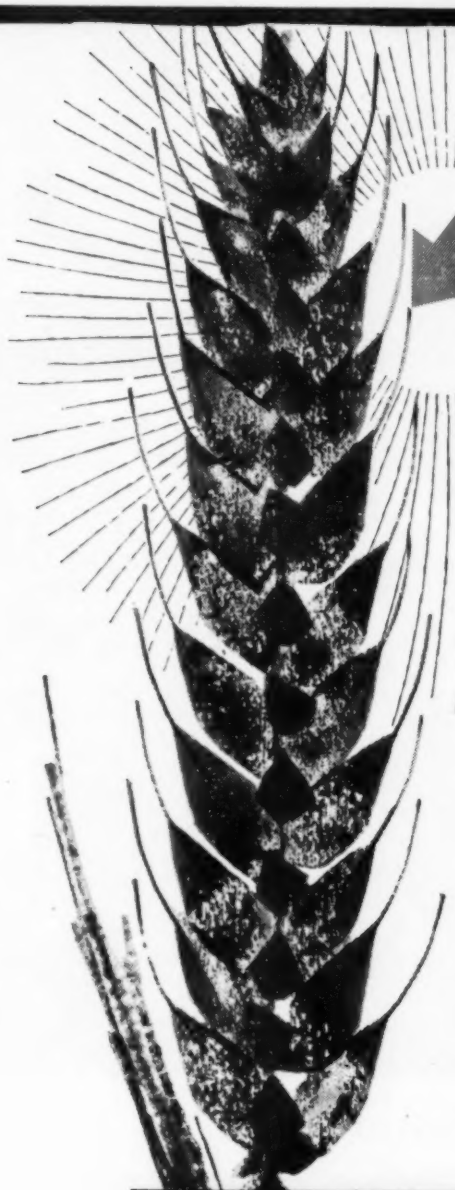
J. HINTON ROBERTSON, M.B., F.R.C.S.Ed. F.R.F.P.S.

Mr. J. Hinton Robertson, consulting surgeon to the Victoria Infirmary, Glasgow, died in the hospital on September 12. He was 67 years of age.

James Hinton Robertson was born in Glasgow on November 26, 1890, the elder son of John Robertson, a writer in the city. Receiving his early education at Queen's Park School, he entered the University of Glasgow as a student of medicine in 1907. He gained numerous prizes and distinctions during his course, and graduated M.B., Ch.B., with honours, in 1912, being awarded the Brunton Memorial Prize, which is given to the most distinguished graduate of the year. His resident posts were served in the Victoria Infirmary, where he was later to do the bulk of his life's work. Then followed a sea trip to the East. On his return, the clouds of the first world war were gathering. He joined the French Red Cross early in the war and served in France for about eighteen months. Returning home, he joined the R.A.M.C. and served first in the Dardanelles campaign and later in East Africa. Demobilized early in 1919, he married Mora MacLeod, a daughter of the manse, and entered general practice at Strichen, in Aberdeenshire. After four years in this country practice he was invited to return to Glasgow and join the surgical staff of the Victoria Infirmary. In 1925 he was elected to the F.R.C.S.Ed. and to the surgical Fellowship of the Royal Faculty of Physicians and Surgeons of Glasgow. For the next thirty years, until his retirement under the age limit in 1956, he practised as a general surgeon. In 1929 he was appointed surgeon to the Broadstone Memorial Hospital in Port-Glasgow and was responsible for all the surgical work there until 1945. He was an honorary lecturer in clinical surgery in the University of Glasgow, and a past-president of the Glasgow Medico-Chirurgical Society and of the Southern Medical Society. In his latter years he was closely identified with the board of management of the Glasgow Victoria hospitals and was convener of the medical committee.

R. M. writes: The death of Hinton Robertson has removed one of the most loved and respected figures in the medical community of the West of Scotland. It is difficult to convey adequately the special esteem in which this quiet, gentle, courteous man was held by all his colleagues, friends, and patients. This was based on his complete unselfishness and unworldliness, so that he sought no personal advancement and dedicated himself entirely to the service of his fellows. He was a most gifted surgeon, sound in judgment, deft and rapid in technique: he had the satisfaction of knowing that the quality of his work was recognized and appreciated, for he was in almost constant demand for the treatment of doctors and their families. He was a most astute clinical observer, and a lot of his surgical work showed striking originality of thought and performance. Yet the publication of his results never attracted him, and his writings and addresses always had a historical or philosophical trend. He was widely and deeply read in all manner of subjects and was generally regarded as the most erudite and cultured of all his medical contemporaries. His conversation was a delight. His great stores of factual knowledge were blended with wisdom and philosophical reflection, and the whole was enhanced by quotation, anecdote, and humorous overtones. Even such a prosaic matter as the reading of a treasurer's report could by the subtle alchemy of Hinton Robertson's whimsical humour and choice of words become transmuted into an unforgettable performance. He was an excellent public speaker, but used his wonderful gift comparatively seldom, and then usually to redress a grievance or to speak on behalf of a younger colleague.

Hinton Robertson was a great clinical teacher of students and the soul of kindness to his juniors, who worshipped



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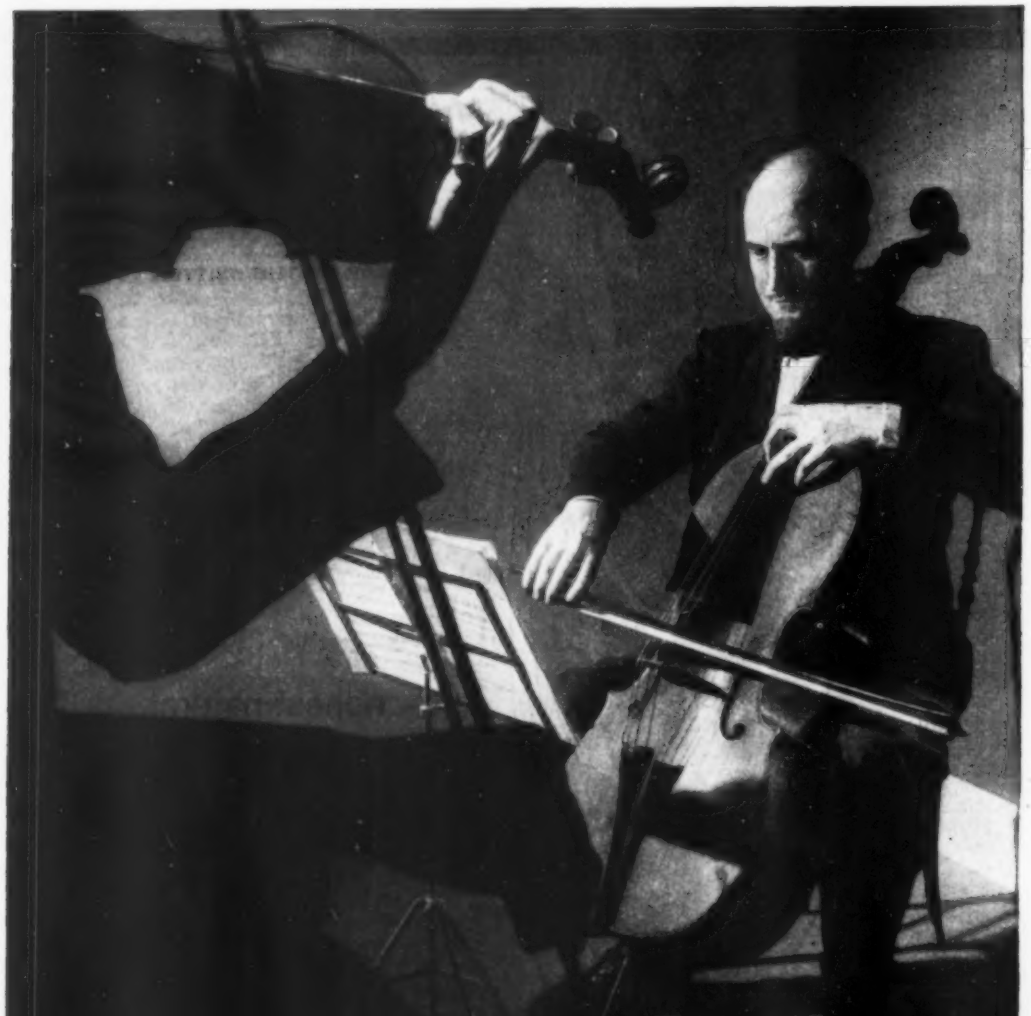

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him. He was a man of deep religious conviction and his whole life had something of a saintly quality. Yet there was nothing priggish about him, and no one was more tolerant towards the weaknesses and shortcomings of his fellow man. No one had ever heard him utter an angry word even under extreme provocation, though he was a very sensitive man and could be readily hurt. To his colleagues in the hospital he was a tower of strength. They took all their problems to him—professional and personal—and they were always sure of enlightenment and balanced judgment and sympathetic understanding. The same balanced judgment was shown in his deliberations in the board of management of the hospital. Hinton Robertson was very happy in his home life. His recreation was yachting, and up to a few years ago it was his great joy to spend his holidays in the Clyde area and often further afield with his wife and son. About a year ago his health began to fail, and, though only too conscious of the unfavourable features of his illness, he remained cheerful and active right to the end. As we take leave of this much-loved man, surely for him St. Paul's words to Timothy are not inappropriate. "I have fought a good fight, I have finished my course, I have kept the faith." To his widow, his son, and his grandchildren we offer our sincere sympathies.

GEORGE FEGLER, M.D.

Dr. George Fegler, who had had a distinguished career as a pathologist and physiologist both in Poland and in this country, died at Addenbrooke's Hospital, Cambridge, on September 23 after a short illness. He was 59 years of age.

George Fegler was born on February 2, 1889, at Cherson, in the Ukraine, of Polish parents and was educated at Odessa and Warsaw. From 1918, when he had enlisted and been taken prisoner of war in Germany, until 1937, when he became professor of experimental pathology in Cracow, he was attached to the Polish Army. He gained his doctorate in medicine in 1924, and was subsequently on the staff of the Chemical Defence Institute. Later he became director of the physiological laboratory in the Aero-Medical Institute. Over the same period he also taught in the physiology department at Warsaw University. In 1939 he was elected to the chair of physiology at Vilna, but on the outbreak of war he was recalled to the Army and with the Polish Forces escaped via Rumania to France and later to Britain. At Edinburgh from 1941 to 1946 he was professor of physiology in the Polish School of Medicine and joined in war research projects already under way in the university's department of physiology. For the next four years before moving to Babraham he continued to do research at Edinburgh supported by grants from the Agricultural Research Council. He became a British citizen in 1949 and his name was put on the permanent *Medical Register* in 1950. For the last eight years of his life he held an appointment as principal scientific officer at the Agricultural Research Council's Institute of Animal Physiology, Babraham, Cambridge. He is survived by his wife, Jeanne, and by his son, John, who recently qualified in medicine at Edinburgh.

C. O. H. writes: Fegler's career was an unusually varied one. His research and more than 40 publications covered problems in haematology, neurochemistry and toxicology, and respiratory, aviation, and high-altitude physiology, while most recently he had made some significant contributions to the physiology of the circulation. Circumstance rather than choice dictated his wide range of interests. The compelling and lasting interest of his life was in the physiology of respiration and circulation, but it was only in the last few years of his life that he could work on problems of his own choice without interruption. During that time he was able to develop an original and very useful method of measuring blood flow and had begun to exploit this in a larger programme to investigate the quantitative relation between blood flow and metabolic rate of individual tissues. As a scientist he was remarkable for a tenacity of purpose which enabled him to overcome obstacles that might sometimes seem insuperable to his colleagues. He was also extremely careful to test his ideas fully before he published, and for every experiment that appeared in a paper many more confirmatory ones remained in his files. His claims never exceeded his experimental information, and he was always prepared to take infinite trouble in examining possible errors in his conclusions. Fegler was well liked by his colleagues at Edinburgh and Babraham. They found him a witty and an amusing companion, whose somewhat pessimistic outlook on world affairs was always modified by a sense of humour. His friends will remember him as a man not only learned in science but well read in the world's literature. He was the son of an artist, and was himself an amateur artist and a connoisseur of fine painting.

T. H. SANDERSON-WELLS, M.B.E., M.D.
F.R.C.S.Ed.

Mr. T. H. Sanderson-Wells, consulting surgeon to the Weymouth District Hospital, died at Wells, Somerset, on October 1. He was 87 years of age.

Thomas Henry Wells—he assumed the name of Sanderson-Wells about 1904—was born on March 12, 1871, and was educated at Bloxham School, near Banbury, Oxfordshire. He received his clinical training at the Middlesex Hospital, qualifying M.R.C.S., L.R.C.P. in 1895. In the following year he took the London M.B., and two years later proceeded to the M.D. Obtaining the degree of B.S. in 1918, he was elected F.R.C.S.Ed. in the same year. After qualification he held the appointment of house-physician and, for eighteen months, casualty medical officer at the Middlesex Hospital. Subsequently he became assistant (later, senior) resident medical officer and lecturer to pupil midwives at Queen Charlotte's Lying-in Hospital. He served as a ship surgeon and as a civil surgeon with the South African Field Force before he settled in practice at Weymouth in 1901. Soon afterwards he was appointed surgeon to the Weymouth Sanatorium for Women and Children and to the old Princess Christian Hospital for Women and Children. In 1921 the hospital was amalgamated with the Weymouth Royal Hospital, the two becoming known as the Weymouth and District Hospital. He continued to serve the new hospital until 1925, when he was forced to give up practice to undergo an operation for injuries received in the early days of his career when he was conducting research into the use of *x* rays. On his retirement he was appointed honorary consulting surgeon to the hospital, later becoming its vice-president. During the first world war he served first as a surgeon with the British Red Cross Hospital at Giza, Egypt, and later as a captain in the R.A.M.C. In 1920 he was appointed M.B.E. for his services in connexion with the work at military hospitals in the United Kingdom during the war.

Food was a subject to which Mr. Sanderson-Wells gave lifelong study. As far back as 1905 we printed in this *Journal* an address he gave to the local Division of the British Medical Association on substitute feeding in infants. In 1938 he endowed an annual lectureship at the Middlesex Hospital Medical School, expressing a wish that the subject to be dealt with should cover the field of the relations between rheumatism and dietetics. He himself gave the inaugural lecture. In the following year he endowed two prizes in the University of London, a senior prize for an essay on some subject bearing on the relation of diet to disease, and a junior prize for an essay on some subject relating to human nutrition. Since 1956 the prizes have been superseded by the Sanderson-Wells Postgraduate Studentship in Nutrition, the available funds being augmented by Mr. Sanderson-Wells in 1952 by a further gift of money. After his retirement he established the Sanderson-Wells Nurses' Prize at the Weymouth and District Hospital, but the funds of this were appropriated by the Minister of Health in 1948 on the inception of the National Health Service. He was a founder-member of the Soil Association,

and a vice-president, formerly chairman, of the Food Education Society. He was the author of *Food and the National Health* (1937) and *Sun Diet* (1939). In 1906 he married Miss Agnes Laurie, whose father rebuilt the Weymouth and District Hospital, the original of which was founded by an ancestor. Mrs. Sanderson-Wells died in 1950. There were no children of the marriage.

A. G. writes: Mr. T. H. Sanderson-Wells did most of his professional work in Weymouth and the surrounding country, where, in addition to his wide general practice, he was surgeon to the Weymouth and District Hospital. His ability, enthusiasm, and keen understanding of human nature contributed greatly to the success of his work. There were many regrets among his patients and colleagues when he retired for health reasons in 1926. He had taken an active part in local affairs, particularly politics. His ability as a speaker was backed by a well-stocked mind. In his retirement he developed his strongly held views on the importance of food in preserving health. He was insistent in his belief that the soil which produces our food either directly or through the animals we eat should not be fertilized by chemicals. Likewise that the food itself should be as free as possible from artificial additions and processes. He had been president of the Food Education Society and a member of the Soil Association. Also he made an endowment for a lecture to be given annually at Middlesex Hospital on a subject concerning soil, plants, animals, and man in relation to food, life, and health. Sanderson-Wells was a public-spirited man with a generous outlook. Many years ago he endowed a substantial fund which provided prizes for the Nurses of Weymouth and District Hospital. Philosopher, patriot, and reformer, he wrote no inconsiderable amount of poetry, which revealed an understanding and tenderness matched only by his insistence upon the virtues of simplicity and steadfastness. The death of his devoted wife eight years ago was a hard blow to him, but such was his energy and resource that he recently complained of his working day being all too short. This is surely a grand state of affairs for a man of 87. His old-world courtesy and charm endeared him to all who met him, even briefly. He was a generous-minded colleague and a staunch friend.

JAMES WATT, M.D., D.P.H.

Dr. James Watt, for many years medical superintendent of King George V Sanatorium, Godalming, Surrey, and chief medical officer of the London County Council's medical tuberculosis service, died at the country branch of St. Thomas's Hospital at Hydestile, Godalming, on October 4. He was within two weeks of his 75th birthday.

James Watt was born in Aberdeenshire on October 17, 1883, the son of William Watt, J.P., and was educated at Robert Gordon's College, Aberdeen, and at Aberdeen University, where he graduated M.B., Ch.B., with first-class honours, in 1908. Outstandingly successful as a student, he held the John Murray scholarship in 1908 and the Anderson scholarship in 1909–10. He took the D.P.H. in 1911, and proceeded to the M.D., with highest honours, five years later. After graduation he was an assistant, first, in the department of pathology, and then in the department of medical jurisprudence in Aberdeen University. From 1912 to 1922 he held a number of appointments in different parts of the United Kingdom: as deputy medical officer of health for the City of Aberdeen; senior resident medical officer at the Royal National Hospital for Consumption and Diseases of the Chest, Ventnor, Isle of Wight; medical superintendent of the Bradford City Fever and Infectious Diseases Hospital; and medical superintendent of the Downs Sanatorium, Sutton, Surrey. From 1922 to 1948, when he retired, he was medical superintendent of the King George V Sanatorium, Godalming, and chief medical officer of the medical tuberculosis service under the old Metropolitan Asylums Board and subsequently under the London County Council. Dr. Watt was president of the Society of Superintendents of Tuberculosis Institutions in 1924 and 1925 and of the Tuberculosis Society in 1926–7. A founder-member of the Joint Tuberculosis Council, he later became its chairman. To his widow and family we tender our sympathy.

We are indebted to Dr. G. Lissant Cox for the following appreciation: The old guard of the original tuberculosis service is thinned again through the death of James Watt, late superintendent of the King George V Sanatorium at Godalming. He was of the pre-1914 vintage, big in body and in mind, contemporary of Ernest Ward, Sir Henry Gauvain, and Jane Walker. Lloyd George's Insurance Act of 1911, with its special financial arrangements for "sanatorium benefit" and for Exchequer grants for sanatoria and dispensaries, stimulated local authorities to provide buildings and the medical staff to run them. Of those very early in the service, James Watt was one. A brilliant student of the Aberdeen school, he was on the high road to a distinguished academic career when he contracted pulmonary tuberculosis. Fortunately, he made a good recovery, and, like several other medical men and women so affected, obtained a junior post in a sanatorium and finally emerged as the well-known head of the large new London County Council sanatorium which has been visited by nearly all who have come to England in order to see some of the best work in tuberculosis. Watt had a clear, lucid, logical mind, and took a prominent part in tuberculosis affairs. One of the two remaining founder-members of the Joint Tuberculosis Council, he later was one of its outstanding chairmen and did valuable work in the chair and on many committees, work both pioneer and advisory in the tuberculosis field. He was a very keen horticulturist, and this hobby was a real solace and interest in his retirement, especially after a serious motor accident had left him grievously lame, though still cheerful and uncomplaining when I last saw him in London. He was the fortunate possessor of the three important qualities, a clear head, a warm heart, and a stiff back, and he used them to the full.

PAULINE M. JONES, M.B., B.Chir.

Dr. Pauline M. Jones was killed in a road accident on September 19. She was 27 years of age.

Pauline Miriam Jones was born on April 27, 1931, and was educated at Wycombe Abbey School, studying medicine at Newnham College, Cambridge, and at St. Bartholomew's Hospital. She qualified by taking the London Conjoint diploma in 1956, and in the same year obtained the degrees of M.B., B.Chir. Since qualification she had held the appointments of house-surgeon and house-physician at Poole General Hospital, paediatric house officer at Odstock Hospital, Salisbury, and senior house officer in paediatrics at the City General Hospital, Stoke-on-Trent.

R. G. J. writes: Since her qualification in 1956 Pauline Jones had practised medicine with enthusiasm, skill, and sympathy. Remembered as a lovely and charming person, she had also a deep faith in God, and an understanding of the needs of other human beings which made her eminently suited to her chosen work. Her many friends will mourn deeply the loss of so promising a life. Our deepest sympathy is extended to her parents in their bereavement.

G. S. KEELING, M.D.

Dr. G. S. Keeling, who was in general practice at Attleborough, Norfolk, for over thirty years, died at the home of his eldest son at Tilehurst, Reading, on September 20. He was 85 years of age.

George Sydney Keeling was born on October 1, 1872. He entered Gonville and Caius College, Cambridge, with an exhibition in 1891, and obtained the B.A., with honours in the Natural Sciences Tripos in 1895. He went on to St. Mary's Hospital with a university scholarship to receive his clinical training, and qualified M.R.C.S., L.R.C.P. in 1898. While at St. Mary's he was awarded prizes in forensic medicine and medical jurisprudence and in ophthalmology. He took the degrees of M.B., B.Chir. in 1900 and proceeded to the M.D. seven years later.

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At first Dr. Keeling seemed destined for a career as an ophthalmologist, for among the appointments he held after qualification were those of senior clinical ophthalmic assistant at St. Mary's and chief clinical assistant at the Royal London Ophthalmic Hospital. He was also clinical assistant at the Hospital for Sick Children, the Brompton Hospital, and the Chelsea Hospital for Women. He contributed an appendix on the normal and pathological histology of the eye to the third edition of Juler's *Handbook of Ophthalmic Science and Practice*, published in 1904. Some of the drawings of microscopic specimens were his work, and he also helped considerably to revise the text of the book.

Dr. Keeling left London in 1906, and for a time was at Bradford, but in 1908 he settled in general practice at Attleborough, where he became also medical officer to the Wayland Union. A member of the British Medical Association for forty years, he was president of the Norfolk Branch in 1931–2 and chairman of the East Norfolk Division from 1938 to 1940. He retired from practice in 1942 and lived in various places in the south of England until 1952, when he went to live at Tilehurst. He is survived by three sons. The eldest, Richard, has followed him into the medical profession.

A. J. B. writes: George Sydney Keeling was a much beloved family doctor and had an extensive practice at Attleborough in Norfolk, to which he gave devoted service for nearly forty years. In spite of being a very hard worker, he managed to find time to keep himself well versed in literature and well up to date in medicine. His intellect was certainly much above the average. In contrast to this brilliance, he was essentially level-headed and imperturbable. He was a man of complete integrity and a staunch churchman. A most likable man, very companionable and easy to get on with, his fellow practitioners showed their respect for him when they elected him president of the Norfolk Branch of the B.M.A.

WALTER JOHNSON, M.B., C.M.

Dr. Walter Johnson, who was in practice in his native Leyland, Lancashire, for almost 60 years, died in a Preston hospital on September 13. He was 85 years of age.

Born on August 29, 1873, Walter Johnson was educated at Preston Grammar School and at Edinburgh University, graduating M.B., C.M. in 1895. After an assistantship in Walkden, Manchester, he returned to Leyland and built up a large and prosperous practice, from which he retired in 1956. He leaves a widow and one son and one daughter. His son is practising medicine in the United States and his daughter is a registrar at Lancaster. To them the sympathy of his many friends and colleagues is extended.

J. S. writes: Walter Johnson was of the real old family doctor type, and was held in high esteem by all. In the early days he used a bicycle to take him on his daily rounds, but later he acquired a one-cylinder Argyll, and was very fond of recalling his adventures as a pioneer motorist in the area. He was at one time police surgeon and a district commissioner of Boy Scouts, a movement in which he was very keenly interested. He certainly was a remarkable man: with great courage he carried on in practice after a complete laryngectomy at the age of 70. He consoled others who had undergone the same operation, taught them to speak, and helped them to take a renewed interest in life.

C. V. ARTHUR, L.M.S.S.A.

Dr. C. V. Arthur died last month in a Paris hospital, to which he had been admitted following a road accident in the city. He was 47 years of age.

Cecil Vernon Arthur was born at Bettws, Ammanford, South Wales, on December 31, 1910. He was educated at Llandovery College before proceeding to St. Mary's Hospital, from which he qualified L.M.S.S.A. in 1939. At the outbreak of the second world war he immediately joined the Royal Navy, and served as a surgeon-lieutenant in the *Warspite* and the destroyer *Hardy*. Invalided out of the Navy in 1943, he spent the next 10 years in a courageous fight to regain his health, and during this time underwent two major thoracic operations. In the last few years Dr. Arthur had been able to practise medicine again, and at the time of his death was casualty officer at Morriston Hospital, Swansea. After such a gallant struggle to regain his health, self-confidence, and enjoyment of living, it seems particularly tragic that he should lose his life in an accident. He married Phyllis Margery Rule in 1947, and our sympathy goes out to her and to her family.—T. O. L.

W. M. McGRATH, M.B., B.Ch., D.P.M.

Dr. W. M. McGrath, senior medical officer at the Leavesden Mental Hospital, died at Abbots Langley Hospital, Hertfordshire, on September 24, after a painful illness. He was 62 years of age.

William Michael McGrath was born in Ireland on December, 17, 1895, and was educated at Castleknock College, Dublin, and at the National University of Ireland, where he graduated M.B., B.Ch. in 1920. After a period in the R.A.M.C. at the Royal Victoria Hospital, Netley, he joined the mental health service of the London County Council in 1921 as assistant medical officer and was appointed to the Cane Hill Hospital, Coulsdon. Later, he was for a time clinical assistant at the Maudsley Hospital. In 1930 he obtained the Diploma in Psychological Medicine of the English Royal Colleges. Appointed senior medical officer to the Leavesden Mental Hospital in 1933, he continued to practise his special branch of medicine both there and at the Abbots Langley Hospital. He was also a visiting psychiatrist to the hospitals for mentally deficient children in the area. In later years he devoted his energy and interests mainly to the growing problem of geriatrics, and organized, developed, and administered the geriatric unit in the Abbots Langley Hospital. The recognized success of this unit remains a final tribute to him. He leaves a widow, to whom all his friends and colleagues extend their sincere sympathy.

W. E. T. writes: Dr. W. M. McGrath was a man with many interests. In his younger days he had many personal successes in various fields of sport, and always retained a sound knowledge of the finer points in hockey, rugby football, and golf. He had a critical mind and strong convictions, but also a keen sense of humour. A deep sympathy and understanding for his patients was one of his most marked characteristics. The welfare of his staff and the development of their interests and amenities were always his concern, and technical training reached a high standard under his constant effort. The regard and affection with which he was held by his staff were genuinely demonstrated by the marked kindness and attention which he received throughout his last illness.

K. S. RICHARD, M.R.C.S., L.R.C.P.

Dr. K. S. Richard, who was in general practice at Welwyn Garden City, died suddenly in London on September 15. He was 48 years of age.

Kurt Simon Richard was born at Dillingen, in the Saar, on December 12, 1909. He studied medicine at Munich University for five years before 1933. He foresaw that he would be unable to sit his finals under the Nazi regime and so came to England, where he continued his medical training at University College Hospital, qualifying M.R.C.S., L.R.C.P. in 1938. After holding the appointment of casualty officer at the London Jewish Hospital, he went into general practice at Welwyn Garden City, where he rapidly established a reputation as a family doctor in the truest sense. He devoted much time to charitable work, and in particular was founder and chairman of the local branch of the "Save the Children" Fund. Besides being an expert bridge player, he was a keen philatelist, and won first prize

for his exhibit of stamps at the Doctors' Hobbies Exhibition. He leaves a widow and two children, and to them we extend our sincere sympathy.

R. V. K. writes: During his 20 years in Welwyn Garden City Kurt Richard gave himself unsparingly to his work. His patients, who regarded him as their friend and philosopher as well as their physician, were all well known to him, and he inspired their confidence and trust by his genuine interest in them as individuals. He will perhaps best be remembered by all who were privileged to meet him for his kindliness. His courage and cheerfulness while facing recurrent ill-health in his later years were tributes to his personality and his spiritual faith.

S. J. CAMPBELL, M.B., F.R.C.S.Ed., D.T.M.

Mr. S. J. Campbell, a surgical specialist in the Malayan Medical Service, died suddenly at Reading on September 23.

Samuel John Campbell was born at Belfast in 1908 and was educated at the Royal Belfast Academical Institute and at the Queen's University of Belfast, where he graduated M.B., B.Ch. in 1930. Four years later he was elected a Fellow of the Royal College of Surgeons of Edinburgh, and in 1938 he took the Liverpool D.T.M. After graduation he held the appointment of resident surgical officer at the Royal Halifax Infirmary. In 1935 he entered the Colonial Medical Service and was posted first to Kedah, then to Brunei, and was in Kuala Lumpur when it was captured by the Japanese in 1942. From 1942 to 1945 he was a prisoner of war in Changi Camp, and after hostilities had ceased became surgeon at Kuala Lumpur. In 1950 he became senior surgeon at Penang, a post which he held until the time of his death. He is survived by his wife, Mary Harling, whom he married shortly after taking up his post in Penang.

P. J. H. writes: Samuel John Campbell had a host of friends scattered all over the world, to all of whom the news of his death will come as a severe blow. His outlook on life was based on firm principles of common sense. He was contemptuous of all frills and pretentiousness, an attitude which was reflected in his professional work, and which made him an admirable teacher. His success in this respect was shown by the number of junior colleagues in the service who had the benefit of his training and obtained their higher degrees in this country. His complete professional honesty made him very humble regarding his own ability, and, although his clinical judgment rarely failed him, he would never hesitate to refer a case if he thought it would be to the patient's advantage. Above all, he enjoyed his life. Keen on all forms of sport, he enjoyed considerable success as a rider at race meetings in Malaya before the war. Most of his friends, however, will remember him as a conversationalist who loved a pithy aphorism, a man of supreme common sense, who was rarely out of humour. He will not be easily replaced in Malaya, and to his widow our sympathy is extended in her sad bereavement.

A colleague writes: The medical profession in Malaya has suffered a sad loss from the sudden death, while on holiday in England, of Sam Campbell, as he was always known to his colleagues. During the war he was interned by the Japanese in Singapore, but after release was soon back at work. At this time he was appointed surgeon to the General Hospital, Penang, where his professional skill was widely appreciated. He combined sound and careful diagnosis with a high degree of operative ability, and he set out to provide in his unit the best possible standards of general surgery. He took a particular interest in training his staff, recognizing the need for each doctor to be prepared for work in isolated parts of the country. Campbell was forthright in his opinions and tolerated poorly any pretentiousness or insincerity, but those who were sick or in trouble could count on his help. In particular he was fond of children and had the happy knack of making friends with those who were brought to him for treatment. His death at a comparatively early age will be greatly regretted by his colleagues, both in the Malayan Medical Service and among the general practitioners of Penang.

ROBERT RUTHERFORD, O.B.E., T.D., F.R.C.S.

Mr. Ronald Macbeth writes: May I be permitted to add a few words to the rather formal obituary on Robert Rutherford which appeared in your issue of September 6 (p. 642)? I doubt if many of his friends were more than vaguely aware of what was, in fact, his first name, since it was as "Jock" that we always knew him. His was one of the more colourful personalities of the King's Medical School of the 1920s. With Scots and Irish in his ancestry, he had a combination of determination and humour, allied with a temper which was easily aroused and as easily quelled. He started on medicine relatively late in life, having already qualified as a dispensing chemist. He found that his post-war pension and gratuity were insufficient to cover his expenses as a medical student, so for a number of years he worked each evening up to midnight in a chemist's shop in the West End, catching the last tram back to his digs. Often the work in the shop was not arduous, and when working for his primary F.R.C.S. he used to make a point of thoroughly digesting at least ten pages of Gray each night. I fancy that he did not always find such learning work easy, because as registrar at King's and superintendent at Hillingdon he seemed to know instinctively the difficulties of surgical comprehension which the younger people might be having, and his teaching was all the more valuable for that reason. He took up his appointment at Hillingdon shortly after the local Board of Guardians had handed control over to the county authorities, and he found a hospital of the workhouse-infirmary type which was scheduled for upgrading under the new regime. To a man with his active imagination and zeal for new ideas this was a heaven-sent opportunity, and he had the satisfaction as superintendent of seeing the work of the hospital expanded out of all recognition. But the pace was too hot for County Hall, and the bureaucratic brake became so irksome to Jock that a parting was inevitable.

When he decided to take a practice on the Borders near his old home town, he had the expectation—partly realized in the days before 1939—of doing much of the surgery of his practice himself. He had dramatic stories to tell of an urgent tracheostomy on a farmer's kitchen table, and of transthoracic drainage of a subphrenic abscess in a shepherd's cottage, miles from the nearest road. This kind of difficulty was the spice of life to Jock, and it is understandable that in the Army he was perhaps a greater success as an officer in charge of a surgical division than as the commanding officer of a hospital. On his return to civilian life he found to his sorrow that there was little or no place in the National Health Service for the surgically active general practitioner, but he found solace in fishing and sketching, at both of which he became a skilled performer. Many of his friends at King's had assumed that a surgical consultant appointment awaited Jock, but I know that in those days of the great slump he did not feel he could afford to wait for something to turn up. He may have had his regrets, but his humour and zest for life induced an ultimate philosophy which made mental capital out of what he had seen and done and prevented his grieving for the might-have-been.

D. N. NABARRO, M.D., F.R.C.P.

Professor J. Henry Dible writes: May I correct one small point in your admirable obituary (*Journal*, October 11, p. 919) of Dr. David Nabarro? You say, "He was also the senior member of the Pathological Society of Great Britain and Ireland." This should read, "*a* senior member." The society was founded in 1906 and Nabarro elected a member in 1913. After more than thirty years' membership he was elected to the class of senior members, to which ordinary members of thirty years' standing are qualified for admission.

Medico-Legal

SELLING OF PROPRIETARY MEDICINES

RESTRICTIVE PRACTICES COURT

On October 13, towards the end of its first hearing, the Restrictive Practices Court declared void the principal restriction under an agreement between members of the Chemists' Federation. This was a restriction which limits the sale to the public of proprietary medicines made by members of the Federation to retail chemists or pharmacists. Here we record the evidence given before the Court; next week we shall summarize counsel's summing up and the Court's findings. Our report is condensed from "The Times" Law Reports.

On October 6 the hearing began, before Mr. Justice Devlin, Mr. Justice Upjohn, Lord Cameron, Sir Godfrey Mitchell, Sir Stanford Cooper, Mr. W. L. Heywood, and Mr. W. G. Campbell, of a reference by the Registrar of Restrictive Trading Agreements regarding an agreement between all members of the Chemists' Federation. The main restriction considered by the Court was one whose paramount purpose was, according to the Federation, to restrict the sale to the public of proprietary medicines manufactured by its manufacturer members to retail chemists or pharmacists. The Federation submitted, relying on section 21 (1) (*a*), (*b*), and (*c*) of the Restrictive Trade Practices Act, 1956, that the restrictions were not contrary to the public interest.

Section 21 (1) of the Restrictive Trade Practices Act provides that ". . . a restriction accepted in pursuance of any agreement shall be deemed to be contrary to the public interest unless the Court is satisfied . . . (*a*) that the restriction is reasonably necessary having regard to the character of the goods to which it applies, to protect the public against injury in connexion with the consumption, installation, or use of these goods; (*b*) that the removal of the restriction would deny to the public as purchasers, users, or consumers of any goods other specific and substantial benefits or advantages enjoyed or likely to be enjoyed by them as such whether by virtue of the restriction itself or of any arrangements or operations resulting therefrom; (*c*) that the restriction is reasonably required for purposes connected with the maintenance of any other restriction . . . found by the Court not to be contrary to the public interest."

Mr. T. G. Roche, Q.C., and Mr. Joseph Dean appeared for the Federation; Mr. Cyril Harvey, Q.C., and Mr. J. R. Cumming-Bruce for the Registrar.

Case for the Federation

Mr. Roche, for the Federation, said that there were 10,500 shops operated by members of the Federation, about 70% of the retailers. There were two big associations of manufacturers, the Federation, which had 122 members, and the Proprietary Association of Great Britain, which had 92, but 23 manufacturers belonged to both. There were also many small manufacturers. Before a manufacturer could join the Federation he had to satisfy the Federation's standards committee that his works and capacity were suitable for the product he proposed to make, and, having been elected, he had to submit his product to the committee and they had to be satisfied as to its suitability, formula, advertising, container, and so on. A manufacturer also had to submit all his products, and, if accepted, they went on to the C.F. List and became subject to the main restriction.

The purpose of this restriction was to prevent the product reaching the public other than through authorized channels. The manufacturer's outlet was not restricted to members of the Federation; any chemist might deal in a C.F. product. Nor did the restriction prevent members from selling non-C.F. products. They were free to stock and sell what they liked, but there were recommendations which advised them to give preference to C.F. products, in display and in recommending, though this was not enforced with penalties.

Value of Chemist's Advice

The Federation relied on paragraphs (*a*) and (*b*) of section 21 (1) in justifying the main restriction. People did go to chemists to seek advice, and a chemist was competent to give advice, either to tell them to go to a doctor or to prescribe something. But a grocer or a druggist was not capable of doing so, and it was of great benefit to the public that it should get proper advice. Further, a person was less likely to ask advice of an unqualified person than of a chemist. He (counsel) was instructed that it was particularly noticeable that those with young children frequently asked advice of chemists. There were also a number of cases where a chemist would give advice when it was not asked—for example, where he knew, through prescriptions, that a member of a family was a diabetic, and could give a warning that a certain product contained sugar or glucose, facts which a grocer might not know, and a grocer might not even know that sugar was bad for diabetics. Another class of case was that of slimming tablets. The Pharmaceutical Society had issued a directive to all chemists not to sell slimming tablets unless on medical advice; that directive did not bind others than chemists, and those products might be sold in grocers' shops. Another danger in the sale of products by non-qualified persons lay in the sale of stomach powders; persons might do themselves injury by going on treating themselves, and an experienced chemist seeing a person repeatedly buying stomach powders, or drastic purges, would take the opportunity of recommending him to go to a doctor.

Mr. Justice Devlin.—You have picked out some products on the C.F. List in regard to which advice is beneficial and there are no doubt more, but it seems to me that you have to justify the whole of the C.F. List. Suppose the restriction is unnecessary in case of 20% of the products, then what do we do? We cannot revise the list.

Counsel said he relied on the over-all effect. If the restriction was removed, the sale of medical goods in non-chemist shops would increase and that was undesirable. There were 2,500 products on the list, and the Federation should not be convicted because some of them were not medicines. He relied on the fact that it was dangerous for people to buy medicines at all except from a chemist's shop and that the public received a benefit in not buying them from unqualified persons. There was also the economic consideration. The small chemist was only just existing on a marginal basis in the nature of £200 a year, and even a small amount of business going to the grocer would make it impossible for him. Another benefit to the public was the examination of proprietary medicines by the standards committee.

Concluding his opening address, counsel said that the main restriction was effective. Since 1939 there had been only two cases where the stop-list had been threatened and one where it had been exercised. The Federation did not exercise pressure on its members.

Kidney Pills and "Aspro"

Mr. R. H. Kemp, secretary of the Chemists' Federation, was then called as the first witness. He had submitted a statement to the Court, and he read an addendum to it describing the events leading up to the formation of the Federation.

Mr. Harvey, cross-examining Mr. Kemp on the second day of the hearing, referred to "B.K. tablets" and "juniper back and kidney pills" on the C.F. List and to advice obtained by the council of the Federation that the constituents of the pills were obsolete and that on medical grounds there was no justification for the products.

Mr. Kemp replied that this was a class of product which for many years had been very popular among a certain class of the public, particularly in industrial areas in the Midlands and the North. The council appreciated the advice as to the undesirable claims made by the manufacturers, but they felt that whatever action they took there would be a continued demand by the class of person accustomed

to self-medication in this way, and that it would be better if the products were distributed under the direction of a pharmacist rather than by a shopkeeper and that, subject to the withdrawal of certain claims, the product should continue on the list.

Counsel.—If someone says that he has kidney trouble and wants these pills, is the pharmacist going to advise him not to buy them?—He would put further questions to the patient and refer him to his doctor. Answering further questions, the witness said that it was not the practice to tell pharmacists that a product on the list had been adversely reported on.

Counsel then produced a packet of aspirin "tabloid" manufactured by Messrs. Burroughs Wellcome & Co. and a packet of "aspro." The witness agreed that chemically and therapeutically they might be regarded as identical; that the Burroughs Wellcome product was sold only in chemists' shops; that aspro was sold largely by chemists; that aspro was also sold in village shops; that as far as it might be foreseen it did not look likely that aspro would be put on the C.F. List, as it was the manufacturer's policy not to do so.

Counsel.—Facing the fact that aspro will continue to be sold in village shops, what public interest is served by the other brand being restricted to chemists' shops?—By virtue of the fact that no extravagant claims are made by the manufacturer for that product. The type of advertising is under the control of the Federation. Re-examined by Mr. Roche, the witness said that, in cases of self-medication, the claims made for a product were of great importance; if there were misunderstanding the pharmacist was better qualified than the grocer to combat it. The standards committee would not have accepted the advertisement of aspro.

Mr. G. E. Mann, M.P.S., a representative of Messrs. Parke Davis & Co. Ltd. on the council of the Federation, was then called. Cross-examined by Mr. Harvey, he said that the back and kidney tablets had been retained on the list because they had been on it originally. The excessive claims made had been amended by the manufacturers, and, provided the tablets were retailed under the control of a pharmacist, there was no reason why they should not be on the list.

Counsel then referred to examples given by the witness in his statement of products which had not been accepted. As to one of those products, counsel said that the reason why it was not on the list was stated to be that it might be dangerous. The reason for keeping the kidney pills on the list was that they might be dangerous, and this product was refused because it might be dangerous. It followed that it could be sold at shops other than chemists' shops, and what was the public benefit in that?

The witness said that the difference between the two cases was that the kidney pills had been on the list originally. This was a new application. He did not accept the suggestion that the interests of the Federation were purely economic.

Mr. A. Aldington, M.P.S., chairman of the Federation's propaganda committee, the next witness, was asked whether he disapproved of "Andrews liver salts" being available to the public in village shops. He said that he thought the public should obtain supplies through pharmacists, who were available to advise if asked; the same applied to "Eno's fruit salts" and to "Kruschen salts." That was the only advantage.

Economic Position of Chemists

Mr. J. Wright, deputy secretary of the National Pharmaceutical Union, then gave evidence relating to the economic position of chemists. In the course of his evidence he said that a statistical survey showed that National Health dispensing did not pay a pharmacist a reasonable salary. A survey conducted in 1953, among 1,000 firms approved by the Government actuary as being a representative sample, showed an average net loss of £152 on National Health dispensing and an average net profit of £355 for other trade, including private dispensing, thus giving the chemist an average net profit of £203 on his combined trade. Even allowing for the £700 shown in the survey as his salary, the witness did not consider it a reasonable reward for a qualified person. There was an area of commodities—hot-water bottles, cameras, cosmetics—in which there was competition with almost everyone, although these goods had been traditionally sold by chemists for years.

Mr. W. T. Rees, M.P.S., a proprietor of old-established pharmacies in and near Cheltenham and a member of the Federation, said in the course of cross-examination that if the C.F. List were abolished the grocers who in their weekly order received demands for pharmaceutical goods on the list would be able to supply them themselves instead of sending to a pharmacist for them, as happened now.

Mr. P. G. Flood, M.P.S., a director of Ferris Chemists (London) Ltd., cross-examined, said that chemists were going to be a lot poorer if the present trend continued. They alone were at the mercy of all classes of trade cutting into their livelihood. The newsagent next door to him had a monopoly of newspapers, and on his shelves near the door was practically every make of proprietary cough mixture, and he was open at 6 a.m. He would like chemists to have the protection which seemed to have been given to every other trader. He could not sell spirits, but the man who sold spirits sold aspro, sometimes from slot machines.

Counsel.—What do retailers get out of the Federation?—We have not time to examine formulae and we have a guarantee in the C.F. List and accept that unjust claims are not made for a product. If the sale of medicines was not restricted to pharmacists, as it was on the Continent, continued witness, it would lead to the extinction of the craft to which he belonged. A chemist in a small town could not live by dispensing alone.

Mr. K. Jenkins, M.P.S., proprietor of the only pharmacy in Bovingdon, said, on the third day of the hearing, that he put the sale of medicines and dispensing at two-thirds of his total business.

Mr. Harvey.—Before you came those people were able to, and did, buy quite a large number of simple household remedies in their local shops? The witness replied that they had, but that when he was preparing to open his shop he found that people were clamouring for a chemist; they were complaining that the products they got were either inadequate or of inferior quality. He agreed that there had been no detriment to the public arising from the fact that before he came they could buy "elastoplast" without having to go three miles. He also agreed that it had been, and still was, a great convenience to the public that they could buy products such as aspirin, "sanatogen," castor oil, "Owbridges lung tonic," "Beecham pills," "milton," salts, and "california syrup of figs" at local grocers.

Counsel.—Is there not a natural tendency among the public to go to a chemist for those kinds of items?

The witness said that the natural tendency of the public was to go to the nearest place. If the restrictions were removed as soon as C.F. products were taken off the list, grocers' wholesalers, hucksters, and newsagents would have them, and he would lose a substantial amount of trade. Patent medicines and C.F. goods showed a large profit margin, and in these days when soap, groceries, and packed bacon had cut margins the grocer would be economically compelled to take other lines. The trade he would lose would be trade in C.F. products advertised to the public. More than half the products on the list were not advertised to the public.

Mr. N. Dewey, M.P.S., general home sales manager of Allen & Hanburys Ltd., and a member of the council of the Federation, in cross-examination by Mr. Harvey, referred to the danger of "ethical" goods—that is, goods not advertised in the Press—being sold by anyone if the policy of the Federation was defeated and the C.F. List abolished.

Pharmaceutical Society's Views

Mr. F. W. Adams, F.P.S., secretary and registrar of the Pharmaceutical Society of Great Britain, said in evidence that he was not a member of the Federation, and in his

opinion it would be harder to control the sale of poisons if the list were abolished owing to the multiplication of channels of distribution. From the view of the society and its statutory duties under the Pharmacy Acts, it was desirable to restrict the sale of medicines to chemists. In reply to Sir Stanford Cooper, the witness said that the society had no machinery for controlling the sale of products outside the category of poisons, other than the statutory powers of discipline it could exercise over pharmacists.

Mr. C. C. Green, assistant secretary of the Federation, gave evidence about proprietary medicines. On cross-examination he said that, out of 9,000 proprietary medicines at present on the market, he estimated that less than one-half were free from statutory control and advertised in the Press; and that, out of 356 firms manufacturing proprietary medicines, 122 belonged to the Federation. If the list were abolished, products not advertised in the Press would be sold by unqualified traders.

Dr. B. A. Young, appointee of the Privy Council on the council of the Pharmaceutical Society, said in evidence that he attached great importance to the discipline exercised over pharmacists by the society and to the traditional standards of chemists. Directives of the society dealing with harmful drugs and laying down moral standards of behaviour were not available to the ordinary shopkeeper who was not subject to them. They exercised a useful control over pharmacists. Witness referred to statements of the society's council about the dangers of the indiscriminate use of slimming drugs, the demand for which had been stimulated by Press publicity. Pharmacists were told not to supply the drugs unless they were satisfied that the drugs were to be used on medical advice. Similarly, methylpentynol, "the wonder drug which promised a date with Rita Hayworth and a salary rise from one's employer," and teething powders containing mercury had been the subject of warnings by the Council.

The pharmacist, because of his training, was quite different from the ordinary shopkeeper, said the witness, and, because of the society's advice on ethics, was subject to useful control. For these reasons only chemists should sell medicines, and it was not proper for this purpose to distinguish between different kinds of medicines.

Registrar's Witnesses

Mr. Harvey, for the Registrar, then called as his first witness Dr. Philip Hamill, who produced lists of C.F. products and comparable non-C.F. products which in his view ought to be available anywhere. He then referred to certain products on the C.F. List which in his opinion should not be generally available because they could be bought for the wrong reasons. The witness agreed that the majority of medicines should only be sold by chemists, but he disagreed with Dr. Young that all medicines should be so restricted.

Dr. Hamill continued his evidence on the fourth day of the hearing. Cross-examined by Mr. Roche, he agreed that a manufacturer might decide not to advertise his goods either because they were unsuitable, or because he wished to make them available for National Health Service prescriptions. He agreed that a trained man could tell into which category a product came.

Counsel.—But a grocer would no more know than the man in the moon?—No.

If a manufacturer is not advertising a product to the public, as a matter of prudence and of protection to the public, is it desirable that it should be screened by a pharmacist?—Yes.

Mr. W. D. Lloyd, a director of Aspro-Nicholas Ltd., then gave evidence.

Cross-examined by Mr. Roche, he agreed that the active ingredient in "aspro" was acetylsalicylic acid, but disagreed that everything aspro could do could be done by any other product containing five grains of acetylsalicylic acid. He said that there were many other brands of aspirin and he would claim that aspro was the finest. The witness's company's acetylsalicylic acid was made for them by a certain company.

Are they the usual trade suppliers?—There are others.

Answering further questions, the witness said that they had increased their sales by selling through all outlets. If they changed their policy the sales might drop and they would like to continue their present policy; nobody stopped them at present. As to the advertisement "Three second action," the witness said that that term was not fully explained in the advertisement; it had been misread, and the advertisement now said that aspro went into action in three seconds. Counsel said that a phrase intended to have one meaning might be read as having another, and that was why the submission of advertisements to an independent body was a great advantage. Witness replied that all their advertisements were submitted to an independent body.

Controls on Advertising

Mr. W. G. Hollis, secretary of the Pharmacists Association of Great Britain, then gave evidence.

Cross-examined by Mr. Roche, he said that their members had to submit not every product but every "advertised" product. Members were asked in the terms of their membership to submit any change in the active ingredients of their formulas, and any new product had to be submitted. The association was consulted even at the development stage. Over the years a number of precedents had been built up, and in simple cases a decision on advertising was taken by him (the witness) with medical consultants; other cases were referred to the committee. The association was one of manufacturers alone.

Mr. B. P. Alton, secretary of the Newspaper Proprietors' Association and its Code of Standards Committee, cross-examined by Mr. Roche, said that the advertisement manager of a newspaper belonging to the association would consult the association about the propriety of an advertisement if there was any doubt, although the final decision was that of the newspaper. The association covered the London newspapers; the Newspaper Society covered the provincial dailies and weeklies, and the Periodical Proprietors' Association the periodicals. They all laid down standards for advertising.

Mr. W. J. Ambrose, assistant managing director of Beecham's Pharmaceuticals Ltd., said in cross-examination that in spite of their substantial resources they had accepted advice from the Pharmacists Association of Great Britain about changes in their medicines. They were subject to the association's control and it was desirable that that control should be extended to all manufacturers. He agreed that when reading some advertisements he had said to himself that they were a bit steep. Apart from conditions as to price, his company did not have any control over their wholesalers. They supplied grocers, drug stores, and others, and he did not consider that those retailers were any more careless in their storage of medicines than chemists.

Sales through Groceries

Mr. H. L. Hamerton, M.P.S., sales director of International Chemical Co. Ltd., of London, a subsidiary of American Home Products Corporation, said his company, though not his parent company, had not joined the Federation, because they considered the restriction of the sale of medicines to chemists undesirable, commercially, as affecting their profits and as interfering with the public convenience.

Mr. A. W. Carter, a proprietor of three grocery shops in and near Reading said his experience was that customers almost invariably asked for products by name. He was sometimes asked whether one medicine was preferable to another, and on rare occasions asked for advice about treatment of ailments. He would never give customers advice, but would always tell the customer to use a medicine which the customer had satisfactorily taken before. Certain C.F. goods were asked for by his customers, and he obtained those products from a chemist. He did not know that "kwells" and codeine were on the poisons list.

Counsel then began their legal submissions to the Court.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 27** (No. 39) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	2	0	0	0		1	0	12	0	2
Dysentery ..	433	64	161	5	4	202	32	124	10	
Encephalitis, acute	3	0		0		7	0		0	
Enteric fever:										
Typhoid * ..	6	1	0	1		9	3	0	0	
Paratyphoid ..	5	2	0	0	4(B)	3	0	0	1	
Food-poisoning ..	347	52	22	2		142	26	39	1	
Infective enteritis or diarrhoea under 2 years				24	53				9	31
Measles *	1,621	120	19	4	55	981	20	15	22	20
Meningococcal infection	10	1	10	2	2	20	0	15	0	
Ophthalmia neonatorum	25	3	3	0		20	1	2	0	
Pneumonia † ..	154	7	96	0	1	1,367	62	603	11	2
Poliomyelitis, acute:										
Paralytic ..	54	6	27	1	5	87	8	7	6	1
Non-paralytic ..	41	4				37	0			
Puerperal fever § ..	221	30	11	0		274	33	7	2	
Scarlet fever ..	543	42	72	17	18	305	25	46	27	13
Tuberculosis:										
Respiratory ..	465	52	84	21		531	70	90	23	
Non-respiratory	66	5	9	4		75	4	8	1	
Whooping-cough..	671	41	68	51	37	564	48	36	4	1

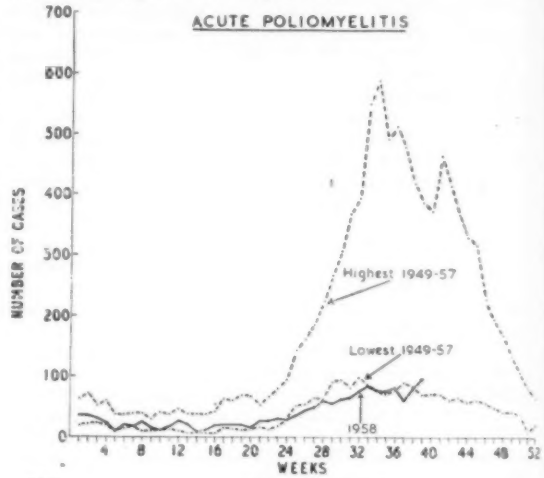
DEATHS	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	No comparable figures available.	0	0	0	0
Dysentery ..	1	0		0			0		0	
Encephalitis, acute		0			0		0	-		0
Enteric fever ..	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	4	0	0	0	0		0	0	0	0
Influenza	4	0	1	0	0		7	28	0	0
Measles		0	0	0	0		0	1	0	0
Meningococcal infection		1	0				0	0		
Pneumonia ..	304	18	10		4		43	29	12	7
Poliomyelitis, acute	2	0		1	0		1		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	63	6	4	2	3		6	6	2	6
Non-respiratory		2	0	0	0		2	0	0	0
Whooping-cough..	0	0	0	0	0		0	0	0	0
Deaths 0–1 year	265	33	21	3	8		23	33	9	13
Deaths (excluding stillbirths) ..	7,978	663	489	100	133		706	670	104	173
LIVE BIRTHS ..	14,097	1192	962	225	361		1197	948	213	398
STILLBIRTHS ..	304	21	17				24	20		

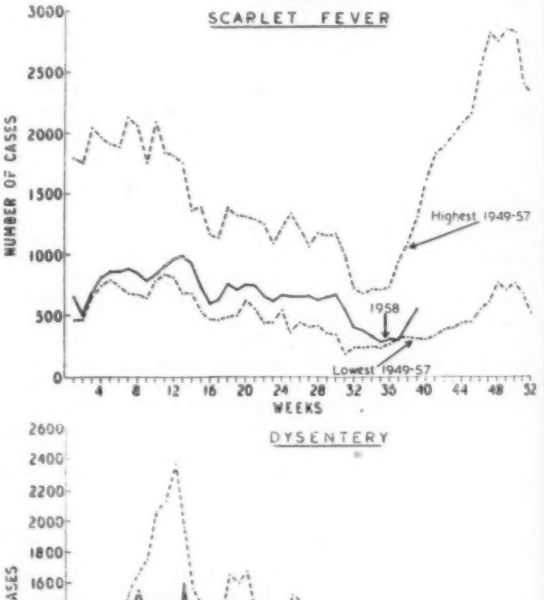
* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

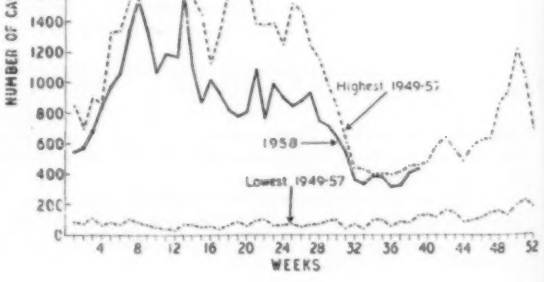
Vital Statistics

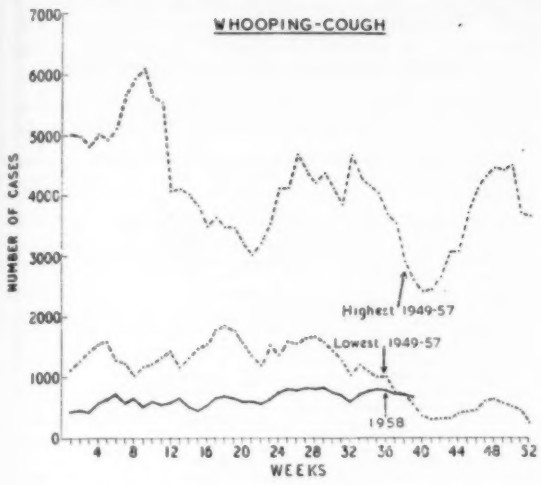
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus - - - - - -, the figures for 1958 thus ————. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









England and Wales in 1957

The deaths during 1957 numbered 514,870 and were 6,461 fewer than in 1956. The deaths were equivalent to a rate of 11.5 per 1,000 population and the rate was 0.2 less than in 1956. The deaths from common infectious diseases were 6 from diphtheria, 10 from scarlet fever, 88 from whooping-cough, and 95 from measles. The age distribution of the 227 deaths attributed to acute poliomyelitis was:

Age in Years	*No. of Deaths*
Under 5	15
5–14	40
15–24	32
25–44	125
45 and over	15
Total	227

The number of deaths from tuberculosis was 4,784, and was 591 fewer than in 1956. Coronary disease accounted for 76,324 deaths, 1,634 more than the total of 1956. The number of deaths from cancer of the stomach was 7,986 for males and 6,009 for females, and these deaths were 239 more for males and 197 fewer for females than in 1956. The deaths from cancer of the lung were 16,430 for males and 2,689 for females, and these totals were 815 more for males and 118 more for females than in 1956. Deaths from violence numbered 21,561 and were 309 fewer than in 1956. Motor-vehicle accidents accounted for 4,898 of these deaths, and this number was 138 fewer than in 1956.

The expectation of life at birth, based on the 1955–7 populations and deaths, was 67.71 for males and 72.39 for females.

Week Ending October 4

The chief fluctuations in the notifications of infectious diseases in England and Wales during the week ending October 4 were rises of 367 for measles, from 1,621 to 1,988, 114 for scarlet fever, from 543 to 657, 57 for acute pneumonia, from 154 to 211, and falls of 120 for whooping-cough, from 671 to 551, 31 for food-poisoning, from 347 to 316, and 26 for acute poliomyelitis, from 95 to 69.

The increase in the incidence of measles was mainly confined to the northern section of the country; the largest rises were 89 in Lancashire, from 304 to 393, 41 in Yorkshire West Riding, from 159 to 200, and 41 in Yorkshire East Riding, from 39 to 80. The largest variation in the returns of scarlet fever was a rise of 27 in Staffordshire, from 29 to 56. The largest fall in the incidence of whooping-cough was 29 in Yorkshire West Riding, from 74 to 45. Five cases of diphtheria were notified, being 3 more than in the preceding week; 4 of these cases were notified in the metropolitan borough of Finsbury.

The notifications of acute poliomyelitis numbered 69, and these cases were 1 fewer for paralytic and 25 fewer for non-paralytic cases than in the preceding week. The largest returns were Yorkshire West Riding 18 (Leeds C.B. 9, Barnsley C.B. 2), Lancashire 11 (Manchester C.B. 4, Oldham C.B. 2, Preston C.B. 2), and Durham 6.

The notifications of dysentery, 442, were 9 more than in the preceding week. The largest returns were Yorkshire West Riding 74 (Leeds C.B. 22, Thorne R.D. 15, Ripon and Batley Bridge R.D. 11), Lancashire 72 (Liverpool C.B. 29), London 51 (Islington 13), and Staffordshire 22 (Kidsgrove U.D. 18).

The largest outbreak of food-poisoning was 23 cases in Southport C.B.

Eire in Second Quarter

The birth rate for the second quarter of 1958 was 22.6 per 1,000 of the population, being 0.2 below the rate for the second quarter of 1957. The infant mortality was 36 per 1,000 registered births and the neonatal mortality was 23; these rates are 4 and 2, respectively, above the rates for the corresponding quarter of 1957. The death rate was 12.6 per 1,000 of the population and was 1.2 above the rate for the second quarter of 1957.

Deaths from the principal epidemic diseases numbered 133 and included 91 from influenza, 35 from gastro-enteritis (under 2 years), 3 from whooping-cough, 2 from measles, 1 from diphtheria, and 1 from acute poliomyelitis. 146 deaths were attributed to respiratory tuberculosis and 28 to other forms of tuberculosis; these deaths were 4 more and 14 fewer, respectively, than the number recorded in the preceding second quarter. Violence accounted for 231 deaths, and 60 of them were due to motor-vehicle accidents.

Medical News

Portrait of Dr. I. D. Grant.—The members and associates of the College of General Practitioners in Scotland are presenting to the College a portrait of its president, Dr. I. D. GRANT, at the Annual Meeting of the College in London on November 22. The portrait will be on view at a reception given by the Scottish Council of the College at the Royal Faculty of Physicians and Surgeons, Glasgow, on October 24, at which Dr. W. S. GARDNER, chairman of the Scottish Council of the College, will preside. Dr. Grant a former chairman of the Representative Body of the B.M.A., is concluding his second year as president of the College of General Practitioners. He has recently returned from a visit to South Africa, where he assisted in plans for founding faculties of the College in the Union.

Leverhulme Research Awards.—These awards are intended for senior workers of established position and are limited to British-born subjects normally resident in the United Kingdom; in exceptional circumstances the Trustees may waive the condition as to residence. No subject of inquiry is excluded from consideration, but preference is given to subjects in which existing provision for research is inadequate. The duration of the awards does not extend over more than two years or less than three months, and the amount depends on the nature of the research and the circumstances of the applicant, who should apply before December 31 to the Secretary, Leverhulme Research Awards, St. Bridget's House, Bridewell Place, London, E.C.4.

Grenfell Christmas Cards.—A pleasant selection of Christmas cards is once again issued by the Grenfell Association to help its medical mission in Labrador. Travel is still mainly by dog team in winter and boat in summer, though aircraft fitted with skis or floats are coming into use. Medical work there continues to increase, particularly in the field of tuberculosis, but the costs remain extremely high. Cards priced from 3d. to 10d., and calendars for a shilling or two, can be obtained from the Secretary, Grenfell Association, 66, Victoria Street, London, S.W.1.

Association of Clinical Biochemists.—At the annual general meeting of the association, held at the Royal College of Surgeons, London, on October 4, the following officers were elected for 1958–9: *President*, Professor E. J. KING. *Chairman*, Dr. A. L. LATNER. *Honorary Treasurer*, Dr. J. H. WILKINSON. *Honorary Secretary*, Dr. A. L. TARNOKY, Royal Berkshire Hospital, Reading.

COMING EVENTS

B.B.C. Television.—"On Call to a Nation," a programme about doctors, October 22, 8.45 to 10 p.m.

North-East London Clinical Society.—Meetings to be held at the Prince of Wales Hospital at 2.30 p.m. on October 23, November 20; January 22, 1959, February 19, March 19. Details from Dr. I. C. GILLILAND, 22, Harley Street, London, W.1.

Society of Medical Officers of Health.—Annual dinner, October 23, at the Royal College of Surgeons. Principal guest Rt. Hon. DEREK WALKER-SMITH, Q.C. Details from the secretary of the Society, Tavistock House South, Tavistock Square, London, W.C.1.

Worshipful Society of Apothecaries of London.—Master's Day Service, Sunday, October 26, at the Church of St. Mary, Aldermary, London, at 11.15 a.m.

Wessex Rahere Club.—Dinner, November 1, at the Grand Spa Hotel, Clifton, Bristol. Further details from Mr. A. DAUNT BATEMAN, 11, The Circus, Bath, Somerset.

Central Mediterranean Forces Surgeons' Club Dinner.—To be held at the Royal College of Surgeons, November 1 at 7 for 7.45 p.m. Tickets £2 per head. Details from Mr. HAROLD BURGE, Bathgate House, 73, Bathgate Road, London, S.W.19.

Glasgow University Club, London.—The annual dinner will be held at the Trocadero Restaurant on November 6 at 7.30 p.m. Glasgow graduates who are not members of the club should write to Dr. J. F. HEGGIE, Department of Pathology, North Middlesex Hospital, Edmonton, London, N.18.

Institute for the Study and Treatment of Delinquency.—Second conference on the Wolfenden Report, November 7–9, at Harrogate. Details from Miss EVE SAVILLE, I.S.T.D., 8, Bourdon Street, Davies Street, London, W.1.

Spiritual Healing.—Four lectures on spiritual healing, November 7, 14, 21, and 28, at St. Mark's Church, Hamilton Terrace, London, N.W.8, at 8 p.m. Details from the vicar, the Rev. W. H. WILSON.

Second Asian Conference of Occupational Health.—November 14–23, in Calcutta. Details from Dr. C. K. RAMCHANDAR, c/o Parry & Co., Ranipet, North Arcot District, Madras.

British Medical Students' Association.—Annual general meeting, November 14–16, at B.M.A. House. Details from the B.M.S.A., B.M.A. House, Tavistock Square, London, W.C.1.

Second Asian-Pacific Congress of Cardiology.—To be held in Melbourne in May, 1960. Further details from Dr. A. E. DOYLE, Alfred Hospital, Melbourne, S.1.

James Mackenzie Lecture.—Dr. G. F. ABERCROMBIE will deliver the James Mackenzie Lecture of the College of General Practitioners on November 22 at 11.30 a.m. in the Great Hall, B.M.A. House, Tavistock Square, London, W.C.1. His subject is "The Art of Consultation."

United Hospitals Choir.—Concert in aid of cancer research, November 25, in the Chelsea town hall. The programme includes works by Mozart, Buxtehude and Handel. Tickets (3s. 6d., 5s., 7s. 6d.) may be obtained from Miss E. SORENSEN, South-western Hospital, Landor Road, Stockwell, London, S.W.9, or at the door.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The Journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Journal of Pharmacology and Chemotherapy.—Issued quarterly (£4 4s. annually). The new issue, Vol. 13, No. 3, includes:

A COMPARISON OF SOME PHARMACOLOGICAL PROPERTIES OF DIOSCORINE AND DIOSCINE. J. L. Broadbent and H. Schnieden.
THE EFFECT OF DRUGS ON SPONTANEOUS MOTILITY AND ON RESPONSE TO STIMULATION OF THE EXTRINSIC NERVES OF THE GUT OF A TELEOSTEAN FISH. G. Burnstock.
SUPERSENSITIVITY OF THE VESSELS OF THE PAROTID GLAND AFTER DENERVATION. P. Öhlin and B. C. R. Strömblad.
LOCAL ACTION OF SOME ANTIBACTERIAL SUBSTANCES AGAINST CORYNEBACTERIUM OVIS IN GUINEA-PIG SKIN. H. O. J. Collier and J. J. Grimshaw.
THE SCHISTOSOMICIDAL AND TOXIC EFFECTS OF SOME ω,ω-DI-(p-AMINOPHENOXY)-ALKANES AND RELATED MONOAMINES. R. F. Collins, M. Davis, N. D. Edge, and J. Hill.
THE TRYPANOCIDAL ACTIVITY OF SOME PYRIMIDYLAMINOPHENYLARSONIC COMPOUNDS. A. D. Ainley and D. G. Davey.
THE EFFECT OF (+)-LYSERGIC ACID DIETHYLAMIDE AND OTHER DRUGS ON THE CAROTID SINUS REFLEX. K. H. Ginzel.
THE ACTION OF CYSTEAMINE AND SYNKAVIT ON GASTRIC EMPTYING IN THE NORMAL AND IRRADIATED RAT. E. V. Hulse.
THE EFFECT OF COOLING AND OF 5-HYDROXYTRYPTAMINE ON THE PERISTALTIC REFLEX OF THE ISOLATED GUINEA-PIG ILEUM. D. Beleslin and V. Varagić.
SLOW-CONTRACTING SUBSTANCES IN HUMAN URINE. K. B. Jensen.
THE MODE OF ACTION OF QUINIDINE ON ISOLATED RABBIT ATRIA INTERPRETED FROM INTRACELLULAR POTENTIAL RECORDS. E. M. Vaughan Williams.
EFFECT OF PYRIDINE ALDOXIMES ON RESPONSE OF FROG RECTUS MUSCLE TO ACETYLCHOLINE. J. H. Fleisher, J. W. Howard, and J. P. Corrigan.
POTENTIATION OF THE RESPONSE OF FROG RECTUS MUSCLE TO ACETYLCHOLINE BY ISOPROPYL METHYL PHOSPHONOFLUORIDATE AND ITS MODIFICATION BY PYRIDINE-2-ALDOXIME METHIODIDE. J. H. Fleisher, J. P. Corrigan, and J. W. Howard.
THE INHIBITORY ACTION OF MORPHINE ON THE CONTRACTION OF THE LONGITUDINAL MUSCLE COAT OF THE ISOLATED GUINEA-PIG ILEUM. H. W. Kosterlitz and Judith A. Robinson.
THE STIMULATORY ACTION OF ACETYLCHOLINE ON ISOLATED RABBIT ATRIA. E. A. Johnson and P. A. Robertson.
PHARMACOLOGICAL PROPERTIES OF ββ-DIMETHYLACRYLOYLCHOLINE AND SOME OTHER β-SUBSTITUTED ACRYLOYLCHOLINES. B. Holmstedt and V. P. Whittaker.
ABSENCE OF RENAL ACTION OF PURE INTERMEDIATE LOBE HORMONE. R. B. Cross.
ACTION OF DIETHYLCARBAMAZINE IN VITRO ON INFECTIVE LARVAE OF WUCHERERIA BANCROFTI. P. Jordan.
THE EFFECT OF SUBSTANCE P ON THE PERISTALTIC REFLEX OF THE ISOLATED GUINEA-PIG ILEUM. D. Beleslin and V. Varagić.
THE CHROMATOGRAPHIC BEHAVIOUR OF WASP VENOM KININ, KALLIDIN, AND BRADYKININ. A. P. Mathias and M. Schachter.
A METHOD OF ASSAYING THE ANTI-TETANUS POTENCY OF DRUGS ON EXPERIMENTAL LOCAL TETANUS IN THE RABBIT. D. R. Laurence and R. A. Webster.
THE ACTIVITY OF A VARIETY OF CHEMICAL COMPOUNDS AGAINST EXPERIMENTAL TETANUS. D. R. Laurence and R. A. Webster.
PHARMACOLOGICAL PROPERTIES OF PEMPIDINE (1:2:2:6:6-PENTAMETHYLPIPERIDINE), A NEW GANGLION-BLOCKING COMPOUND. S. J. Corne and N. D. Edge.
ANTITHYROID ACTIVITY OF THIOHYDANTOINS. R. Kilpatrick, D. T. Elmore, and D. R. Wood.

Journal of Clinical Pathology.—Issued six times a year (£4 4s. annually). The new issue, Vol. 11, No. 5, includes:

TWO CASES OF MARROW FAILURE WITH MASSIVE MARROW PLASMOCYTOSIS SIMULATING MYELOMATOSIS. W. D. Nicoll, A. J. Watson, and J. W. Whitelaw.
THE SYSTEMIC LESIONS OF WHIPPLE'S DISEASE. P. Farnan.
CUTANEOUS PETECHIAE IN FATAL CORONARY ARTERY DISEASE. L. M. Gerlis.
CONGENITAL AGENESIS OF THE SPLEEN WITH CHRONIC ENTEROCOLITIS IN AN ADULT. J. Gordon Alexander.
METHODS FOR THE INVESTIGATION OF THE COAGULATION MECHANISM IN SMALL CHILDREN. David J. B. Ashley.
THE EFFECT OF CITRATE ON EUGLOBULIN METHODS OF ESTIMATING FIBRINOLYTIC ACTIVITY. Monamy Buckell.
THE KAOLIN CLOTTING TIME. J. Margolis.
THE DISTRIBUTION OF CELLS IN PERIPHERAL BLOOD SMEARS. E. Davidson.
FAMILIAL HAEMOPHILIA AND FACTOR VII DEFICIENCY. M. Constandoulakis.
THE CLINICAL EVALUATION OF STAPHYLOCOCCAL ANTI-ALPHA HAEMOLYSIN TITRES IN PATIENTS' SERA. Herta Schwabacher and A. J. Salsbury.
A CRITICAL ASSESSMENT OF THE FREEZE-DRIED DISC TECHNIQUE FOR DETERMINING THE SENSITIVITY OF BACTERIA TO SULPHONAMIDES AND ANTIBIOTICS. C. E. D. Taylor, G. V. Heimer, and C. C. Spicer.
A TRIAL OF RAPPAPORT'S MEDIUM. Patrick Collard and Marian Unwin.
THE INVESTIGATION OF SYMPTOMLESS GLYCOSURIA WITH THE GALACTOSE AND CORTISONE MODIFIED GLUCOSE TOLERANCE TESTS. R. B. Goudie, W. P. Stamm, and S. Dische.
CHEMICAL EVALUATION OF HEPATIC FUNCTION IN NIGERIANS. J. C. Edozien.
COPPER METABOLISM IN NORMAL ADULTS AND IN CLINICALLY NORMAL RELATIVES OF PATIENTS WITH WILSON'S DISEASE. F. C. Neale and M. Fischer-Williams.
THE ESTIMATION OF HIGH CONCENTRATIONS OF PLASMA ACID PHOSPHATASE. E. Bowers and K. W. Denson.
AN EXTRACTION TECHNIQUE FOR THE ESTIMATION OF EVANS BLUE IN PLASMA. Michael Hobsley and Ernest D. Dew.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

Annals of the Rheumatic Diseases.—Issued quarterly (£3 annually). The new issue, Vol. 17, No. 3, includes :

PREVALENCE OF RHEUMATOID ARTHRITIS IN URBAN AND RURAL POPULATIONS IN SOUTH WALES. W. E. Miall, J. Ball, and J. H. Kellgren.
USE OF THE INTRAMUSCULAR ROUTE FOR PREDNISOLONE ACETATE THERAPY. H. F. West.
SUBCUTANEOUS NODULES OF STILL'S DISEASE. E. G. L. Bywaters, L. E. Glynn, and A. Zeldis.
RHEUMATOID DISEASE IN THE LARYNX AND LUNG. G. A. Gresham and T. D. Kellaway.
RECURRENT ATTACKS OF ACUTE RHEUMATISM IN SCHOOL-CHILDREN. R. A. N. Hitchens.
RHEUMATOID ARTHRITIS OF THE CERVICAL SPINE IN THE ADULT. J. Sharp, D. W. Purser, and J. S. Lawrence.
C-REACTIVE PROTEIN IN RHEUMATIC HEART DISEASE. R. D. Eastham, P. Szekely, and K. Davison.
COMPARISON OF THE ERYTHROCYTE SEDIMENTATION RATE, C-REACTIVE PROTEIN, SERUM DIPHENYLAMINE, AND TETRAMMONIUM TESTS IN RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE. R. D. Eastham, P. Szekely, and K. Davison.
VALUE OF URICOSURIC AGENTS AND IN PARTICULAR OF G.28 315 IN GOUT. G. D. Kersley, E. R. Cook, and D. C. J. Tovey.
INVOLVEMENT OF THE NERVOUS SYSTEM IN REITER'S SYNDROME. George W. Csonka.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ● Application should be made first to the institution concerned.

Monday, October 20

EDINBURGH UNIVERSITY.—At Anatomy Lecture Theatre, University New Buildings, 5 p.m., inaugural lecture by Professor John Boyes: Dental Research—Pattern of Progress.
GUY'S HOSPITAL.—At Anatomy Lecture Theatre, 5.15 p.m., lecture-demonstration in endocrinology by Dr. P. M. F. Bishop: Thyrotoxicosis.
●HUNTERIAN SOCIETY.—At Talbot Restaurant, London Wall, E.C., 7 for 7.30 p.m., First Dinner Meeting. 8.30 p.m., Presidential Address by Dr. Francis Leslie: Thirty Years' Experience in General Practice.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. M. Campbell: Results of Surgical Treatment of Pulmonary Stenosis.
●SOCIETY FOR THE STUDY OF ADDICTION.—At Rembrandt Rooms, Thurloe Place, S.W., 7 for 7.30 p.m., annual dinner. Mr. Stephen Potter: Doing Something Elsism—Confessions of a Last Momentist.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF ANATOMY AND EMBRYOLOGY.—At Anatomy Theatre, Gower Street, W.C., 5.30 p.m., Dr. E. Gutmann (Czechoslovakia): Nervous Regulation of the So-called 'Trophic Processes' in Striated Muscle.

Tuesday, October 21

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor C. H. Stuart-Harris: Adenoviruses and Respiratory Disease in Man.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. Pegum: Hair Growth.
LIVERPOOL UNIVERSITY: FACULTY OF MEDICINE.—At Large Lecture Theatre, New Medical School, Ashton Street, 5.15 p.m., Mr. R. C. J. Hill (Durban): Tuberculosis in the Bantu.
MANCHESTER UNIVERSITY, DEPARTMENT OF OCCUPATIONAL HEALTH AND NORTH-WEST ENGLAND FACULTY, COLLEGE OF GENERAL PRACTITIONERS.—At Theatre 1, Clinical Sciences Building, York Place, 8.30 p.m., Problems Encountered on the Return to Work.
ST. ANDREWS UNIVERSITY.—(1) At Physiology Department Lecture Theatre, 5 p.m., Dr. B. L. Andrew: Aims and Methods in Neurophysiology. (2) At Physiology Lecture Theatre, 6 p.m., Dr. Sydney Blackman: Radiological Study of Swellings in the Lower Jaw.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Dr. Shila Ransom: Analgesic Drugs Used in Labour.
SOCIETY FOR THE STUDY OF ADDICTION.—At Medical Society of London, 8 p.m., symposium: Use and Abuse of Tranquillizers. Opening speaker, Professor A. D. MacDonald. Other speakers, Dr. J. C. Batt and Dr. T. H. Howell.
SOUTH-WEST LONDON MEDICAL SOCIETY.—At Bolingbroke Hospital, 8.30 p.m., Dr. A. Kahan: Some Aspects of Obesity and Diabetes.
UNIVERSITY COLLEGE LONDON.—At Anatomy Theatre, Gower Street, W.C., 1.15 p.m., Dr. D. R. Wilkie: Man-powered Flight.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr J. Minton: Ocular Manifestations in Clinical Neurology (Part II).

Wednesday, October 22

BRITISH PSYCHOLOGICAL SOCIETY: MEDICAL SECTION.—At Royal Society of Medicine, 8.30 p.m., Dr. Marie Jahoda, Ph.D.: Current Concepts of Mental Health.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Benign Skin Tumours of Ectodermal Origin.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. R. May: Place of *H. influenzae* in Chronic Respiratory Infections.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, 4.30 p.m., Guest lecture by Professor H. C. McLaren: Diagnosis and Treatment of Carcinoma *in situ*.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. A. Clifford Morson: Non-tuberculous Infections of the Urinary Tract.
LIVERPOOL UNIVERSITY: FACULTY OF MEDICINE.—At Large Lecture Theatre, New Medical School, Ashton Street, 5.15 p.m., Sir Ronald Fisher, Sc.D., F.R.S.: Smoking and Cancer.
LONDON UNIVERSITY.—At Institute of Dental Surgery, Eastman Dental Hospital, 5 p.m., special university lecture by Dr. J. J. Pindborg (Copenhagen): Classification of Odontogenic Tumours.
MANCHESTER MEDICAL SOCIETY.—At Physiology Theatre, Medical School, Manchester University, 4.30 for 5 p.m., Presidential Address by Dr. F. R. Ferguson: Neurology—Bridging the Gap.
PHARMACEUTICAL SOCIETY OF GREAT BRITAIN.—7.30 p.m., Dr. A. H. Beckett, Ph.D.: Pharmaceutical Research in the United States.
PLYMOUTH MEDICAL SOCIETY.—At Duke of Cornwall Hotel, annual dinner and dance.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Guest lecture by Professor C. H. Gray: Role of the Endocrine Organs in Diabetes Mellitus.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Surgeon Rear-Admiral S. G. Rainsford: Ionizing Radiations in Industry—The Medical Problem (illustrated).
●SOCIETY OF BRITISH NEUROLOGICAL SURGEONS.—At London Hospital, 5.30 p.m., 1st Hugh Cairns Memorial Lecture by Sir Geoffrey Jefferson, F.R.S.: Sir Hugh Cairns.

Thursday, October 23

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. D. G. Evans: Vaccination Against Poliomyelitis.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Sebaceous Glandular System.
ROYAL SOCIETY OF HEALTH.—2.30 p.m., Dr. P. J. Lawther, Dr. S. G. Burgess, Ph.D., and Mr. C. W. Shaddick: Bronchitis in Relation to Air Pollution.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Sir Paul Mallinson: postgraduate demonstration in psychiatry.

Friday, October 24

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr H. J. Wallace: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. E. H. Hudson: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Guest lecture by Professor C. V. Harrison: Pathology of Malignant Lymphomas.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 4.30 p.m., Guest lecture by Professor W. I. C. Morris: Mechanism of Blood Coagulation and its Obstetric Disorders.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Guest lecture by Mr. F. B. Cockett: Surgery of Venous Ulceration of the Leg (and silent colour film). (2) 4 p.m., Guest lecture by Dr. D. A. K. Black: Renal Circulation.

Saturday, October 25

ASSOCIATION OF ANAESTHETISTS OF EDINBURGH.—At Adam House, Chambers Street, 6 p.m., Mr. B. T. le Roux: Extracorporeal Circulation.

APPOINTMENTS

MANCHESTER REGIONAL HOSPITAL BOARD.—C. St. J. Davies, M.R.C.S., L.R.C.P., D.M.R.D., Whole-time Consultant Radiologist, Stockport and Buxton Group of Hospitals; G. H. Waddington, M.R.C.S., L.R.C.P., D.M.R.D., Maximum Part-time Consultant Radiologist, Bolton and District Group of Hospitals; J. A. Carr, M.D., F.R.C.S., Consultant Surgeon (eight half-days weekly), Bury and Rossendale Group of Hospitals; R. A. Daws, F.R.C.S., F.R.C.S.Ed., Consultant Surgeon (nine half-days weekly) based on Preston and Lancaster; R. J. Calvert, M.D., Ph.D., M.R.C.P., D.P.H., Maximum Part-time Consultant Physician, Burnley and District Group of Hospitals; R. W. Buckley, M.B., Ch.B., F.F.A. R.C.S., Maximum Part-time Consultant Anaesthetist, Macclesfield and District Group of Hospitals; J. O'Neill, M.B., B.S., M.R.C.P.Ed., D.P.M., Maximum Part-time Consultant Psychiatrist, Ashton, Hyde and Glossop Group of Hospitals; V. J. Keating, M.B., B.Ch., F.F.A. R.C.S., Maximum Part-time Consultant Anaesthetist, Burnley and District Group of Hospitals; D. P. Oakley, M.B., Ch.B., D.P.M., Whole-time Assistant Psychiatrist (S.H.M.O.), Whittingham Hospital; A. M. Danziger, M.R.C.S., L.R.C.P., D.A., and Helen L. S. Tennent, M.B., Ch.B., D.A., Whole-time Assistant Anaesthetists (S.H.M.O.), North Manchester Group of Hospitals.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—P. J. van den Brul, M.B., B.S., Anaesthetic Registrar to Bath Group of Hospitals; F. Williamson, M.D., Surgical Registrar, Torbay Hospital, Torquay, and Newton Abbot Hospital; D. I. Stirk, F.R.C.S., Consultant Surgeon in Exeter Clinical Area with duties in North Devon, mainly at the North Devon Infirmary, Barnstaple.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Pattinson.—On October 7, 1958, at South Molton, Devon, to Dr. Maureen F. (formerly Davies) and Roger T. Pattinson, L.D.S. R.C.S., a daughter—Jean Lindsey.
Stone.—On September 27, 1958, at Wanganui, New Zealand, to Barbara Mary (formerly Dana), M.B., B.S., wife of Arthur Richard Stone, M.R.C.P., M.R.A.C.P., a son.

MARRIAGES

Dodd—Gardner.—On September 29, 1958, at Edinburgh, Keith Dodd, D.S.C., M.R.C.S., L.R.C.P., D.A., of Bishop's Stortford, Herts, to Elizabeth Gardner, of Edinburgh.

DEATHS

Atthill.—On September 27, 1958, Frank Atthill, M.R.C.S., L.R.C.P., of Great Bentley, Essex, aged 82.
Bamford.—On September 25, 1958, Rachel Ethel Bamford, M.B., B.Ch., of 27, Nevill Road, Hove, Sussex.
Buchan.—On September 24, 1958, at Station Road, Laurencekirk, Kincardineshire, Thomas Kirkland Buchan, M.B., Ch.B.
Campbell.—On September 23, 1958, at Reading, Berks, Samuel John Campbell, M.B., F.R.C.S.Ed., D.T.M.
Cherry.—On September 11, 1958, the result of an accident, Alan Percival Cherry, M.B., B.S., of Largs Bay, South Australia, aged 41.
Connold.—On September 23, 1958, at his home, 9, Station Road, Biggleswade, Beds, the Reverend Thomas Allan Lane Connold, M.R.C.S., L.R.C.P., aged 62.
Fegler.—On September 23, 1958, at Addenbrooke's Hospital, Cambridge, George Fegler, M.D., of 24, The Close, Babraham, Cambridge, aged 59.
Flowers.—On September 26, 1958, at St. George's House, Harrogate, Yorks, Wilfred Stephen Flowers, M.B., Ch.B., aged 60.
Green.—On September 21, 1958, Alexander McWatt Green, M.B., Ch.B., of Rosyth House, Bo'ness, West Lothian.
James.—On September 20, 1958, Frederick William James, M.R.C.S., L.R.C.P., of 2, Peaks Hill, Purley, Surrey, aged 86.
Landor.—On September 12, 1958, at Woollahra, New South Wales, Australia, Joseph Victor Landor, M.D., M.R.C.P., D.P.H., D.T.M.&H.
McGrath.—On September 24, 1958, at Abbots Langley Hospital, near Watford, Herts, William Michael McGrath, M.B., B.Ch., D.P.M.
Madden.—On September 24, 1958, at Rush Green Hospital, Romford, Essex, Cyril Paul Madden, L.M.S.S.A.
Roberts.—On September 24, 1958, at Ravenscraig, Ardrossan, Ayrshire, Harry Miller Roberts, L.R.C.P.&S.Ed., L.R.F.P.S., aged 80.
Taylor.—On September 24, 1958, at Marksbury, Bath, Som, William Peach Taylor, M.B., Ch.B., aged 92.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Surgical Treatment for Asthma

Q.—*What is the present position of surgical treatment for asthma, including that of vagus interference?*

A.—Surgical treatment for asthma is in abeyance. The removal of a localized area of infection such as bronchiectasis should decrease the frequency and severity of attacks. The results have not been reliable, and for this reason operating needs much judgment and experience. Bilateral division of the vagus does not relieve asthma in most cases. In many patients both lungs have been stripped of all nerve connexions save those of the walls of bronchus, artery, and veins. Asthma has not been relieved for more than a short time in the large majority of cases. Occasionally tracheotomy with removal of obstructing secretions may be life-saving and may maintain the patient until the acute attack has passed.

References

Abbott, O. A., Hopkins, W. A., and Guilfoil, P. H., *J. thorac. Surg.*, 1950, **20**, 571.
Blades, B., Beattie, E. J., jun., and Elias, W. S., ibid., 1950, **20**, 584.

Psoriatic Arthritis

Q.—*Is there a name for the syndrome of peripheral rheumatoid arthritis associated with psoriasis? What is the treatment?*

A.—There has been considerable difference of opinion in the past on the significance of the association of psoriasis with arthritis of the rheumatoid type. Both are fairly common conditions and chance association of the two is not unlikely. However, the majority of rheumatologists now agree that psoriasis occurs in about 3% of patients with polyarthritis of the rheumatoid type[1] as compared with 0.7% in the general population.[2] In a careful study of 42 patients with psoriasis and arthritis, compared with 55 unselected cases of rheumatoid arthritis in whom the differential agglutination test (D.A.T.) was positive, and 310 cases of uncomplicated psoriasis, Wright[3] concluded that the group of patients with psoriasis and an erosive form of arthritis showed a sufficient number of distinctive features to warrant the assumption that this combination of lesions was a definite clinical entity. The D.A.T. was negative in 94% of these cases. Nail changes were present in 87%. The distal interphalangeal joints were commonly involved, but were never the only joints affected. Subcutaneous nodules were found in only one patient in whom the D.A.T. was positive. The clinical picture of ankylosing spondylitis was present in three patients. The course of the disease was milder than those of rheumatoid arthritis (complete remissions occurred in 50%). Stiffness rather than pain was the major complaint in the majority of patients. Changes in the nails bore a closer relationship to the onset and course of the arthritis than the skin lesions, and the arthritis was less often polyarticular at onset than in classical rheumatoid arthritis. The name psoriatic arthritis would therefore appear to be an appropriate descriptive term for this syndrome.

With regard to treatment, the measures used in rheumatoid arthritis are applicable—i.e., full doses of aspirin, prevention of deformity by the use of splints, physiotherapy and active exercises. Gold is well tolerated in more severe cases. In view of the generally mild course, the use of steroids or corticotrophin is seldom indicated.

References

1 Bauer, W., *New Engl. J. Med.*, 1939, **221**, 524.
2 Ingram, J. T., *Brit. med. J.*, 1954, **2**, 823.
3 Wright, V., *Ann. rheum. Dis.*, 1956, **15**, 348.

Delayed Ligation of Cord

Q.—*What is the rationale of delayed ligation of the umbilical cord?*

A.—As a result of their cineradiographic studies of the circulatory changes at birth in the sheep, Barclay, Franklin, and Prichard[1] concluded that blood continued to flow along the umbilical vein through the ductus venosus for a few seconds after pulsation and circulation had ceased in the umbilical arteries at the base of the cord. They estimated that in the interval between the closures of the umbilical arteries and of the ductus venosus about 100 ml. of blood was gained by the foetus from the placenta.

In the human, about one-quarter of the total foetal blood volume at or near term lies in the placenta and cord. DeMarsh, Alt, and Windle[2] showed that clamping the cord immediately at birth deprived the baby of this 90–140 ml. of blood. Delay in ligating the cord until pulsation had ceased enabled about half of this blood to be regained by the foetus, while if the cord was not clamped until the placenta had separated, and the baby held below the level of the mother so that gravity assisted, about 75% of this blood was regained. These findings have been confirmed by others for both vaginal[3 4] and abdominal[5] delivery.

The baby may make appropriate adjustments according to the amount of blood recovered from the placenta, for when the cord is clamped early the baby's blood subsequently shows a higher reticulocyte count. But delayed ligation is now generally practised, especially in the premature baby, in whom the extra blood may help to maintain blood pressure and to whom the iron in the returned red cells is particularly valuable; but in all neonates the added blood volume may increase output from the right ventricle by augmenting venous return.

References

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Corrections.—The references in Dr. E. F. B. Cadman's article on Cullen's sign (*Journal*, September 20, p. 718) included two to *Trans. New Engl. obstet. gynec. Soc.* The journal should have been the *Transactions of the North of England Obstetrical and Gynaecological Society*. The references should therefore have read: Galloway, W. D. (1939). *Trans. N. Engl. obstet. gynaec. Soc.*, 1937, p. 56. Gough, W. (1939). *Trans. N. Engl. obstet. gynaec. Soc.*, 1937, p. 56.

We regret that we quoted the writer of the letter on "Midwifery Bag" ("Notes and Comments," October 4, p. 868) as Dr. A. Goodman. It should have been Dr. M. Goodman.

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